AGA Technical Review on Nausea and Vomiting

This literature review and the recommendations therein were prepared for the American Gastroenterological Association (AGA) Clinical Practice and Practice Economics Committee. The paper was approved by the committee on March 4, 2000, and by the AGA governing board on May 21, 2000.

Nausea and vomiting are common and distressing symptoms with a number of underlying causes. They are somewhat unique among gastrointestinal symptoms in that on the one hand they may represent a basic, physiologic homeostatic response to an ingested exogenous toxin; on the other hand, they may indicate a disease process of the gastrointestinal tract, adjacent organs, or central nervous system (CNS). Given the number and variety of diagnostic possibilities, it would appear that the clinical approach to the patient with nausea and vomiting may prove daunting. In practice, however, an appreciation of the principal causes of nausea and vomiting in various clinical contexts, combined with careful attention to the patient's history and physical examination and some relatively simple investigations, should lead to a clear diagnosis of the cause of the patient's symptoms in most cases. With the recognition of the primary cause, whether it be an acute enteric infection, pregnancy, or an exogenous toxin, most instances of acute nausea and vomiting can be readily resolved. Chronic nausea and vomiting, usually defined as the persistence of these symptoms for more than 1 month, often present a greater clinical challenge, in some instances because of failure to isolate the basic cause and in others because of inability to satisfactorily suppress symptoms.

In this review, when dealing with the evaluation and management of nausea and vomiting, we differentiate between patients with relatively acute presentations, and those, albeit less common, instances of chronic, unexplained symptoms. Nausea and vomiting are also among the symptoms included in the definition of dyspepsia; because the evaluation and management of dyspepsia have been dealt with in detail in another review in this series,[1] they are not explored in any detail in this review, which limits its discussion to the symptoms of nausea and vomiting per se. The literature on which this review was based was selected, using MEDLINE, as follows: all references from 1965 to the present that included nausea and vomiting in the title, were in English, and dealt with human subjects (n = 1073); all references from 1996 to the present that included the terms *nausea*, *vomiting*, and *therapy* anywhere (n = 1262); and references derived from review articles, book chapters, etc., that dealt with nausea and vomiting in general or with specific diagnostic or therapeutic issues.

Definitions

Before reviewing the evaluation and management of nausea and vomiting, it is important to be clear on their definitions, the definition of related symptoms, and, in particular, their differentiation from a number of other symptoms prone to cause confusion (Table 1). *Nausea* is entirely subjective and is commonly described as the sensation (or sensations) that immediately precede vomiting. Patients state that they feel as if they are about to vomit, or use such terms as "sick to the stomach" or "queasy." *Vomiting*, in contrast, is a highly specific physical event that results in the rapid, forceful evacuation of gastric contents in retrograde fashion from the stomach up to and out of the mouth. In vomiting, nausea is followed by *retching* (repetitive active contraction of the abdominal musculature). These contractions generate the pressure gradient that leads to evacuation, the most clearly recognized component of vomiting. Retching may occur in isolation without discharge of gastric contents from the mouth. It is important to emphasize that vomiting is a complex physiologic process, described in detail below, that includes both involuntary and voluntary components. Although usually preceded by nausea, vomiting may occur in the absence of nausea in some settings. Vomiting must be distinguished from *regurgitation*, which is passive by definition and describes the retrograde flow of esophageal contents into the mouth. Acid regurgitation, for example, is a cardinal symptom of gastroesophageal reflux. *Rumination*,[2] a phenomenon that may easily be confused with vomiting, is defined as the effortless regurgitation of recently ingested food into the mouth, followed by rechewing and reswallowing or

Abbreviations used in this paper: CNS, central nervous system; EGG, electrogastrography; 5-HIAA; 5-hydroxyindole acetic acid; HT_3, 5-hydroxytryptamine$_3$; PCNV, postchemotherapy nausea and vomiting; PONV, postoperative nausea and vomiting; SBFT, small bowel follow-through.

0016-5085/01/$10.00
doi:10.1053/gast.2001.20516

Table 1. Some Definitions of Terminology

Vomiting	Forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature
Nausea	The unpleasant sensation of the imminent need to vomit, usually referred to the throat or epigastrium; a sensation that may or may not ultimately lead to the act of vomiting
Regurgitation	The act by which food is brought back into the mouth without the abdominal and diaphragmatic muscular activity that characterizes vomiting
Anorexia	Loss of desire to eat, that is, a true loss of appetite
Sitophobia	Fear of eating because of subsequent or associated discomfort
Early satiety	The feeling of being full after eating an unusually small quantity of food
Retching	Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, referred to as "dry heaves"
Rumination	Chewing and swallowing of regurgitated food that has come back into the mouth through a voluntary increase in abdominal pressure within minutes of eating or during eating

spitting out. This is a passive phenomenon. It is not preceded by nausea and does not include the various physical phenomena associated with vomiting. As recently emphasized by O'Brien et al.,[3] rumination typically begins within minutes of a meal, is usually repetitive, and is rarely associated with retching, but it may be accompanied by weight loss and bulimia. Although originally described among mentally retarded children and those with psychiatric illnesses, it has become clear that rumination can occur in adults and in the absence of either of these entities.[2–4] *Dyspepsia* is most commonly defined as chronic or recurrent pain or discomfort centered in the upper abdomen.[1] Although other symptoms such as nausea, vomiting, early satiety, and fullness may be associated with dyspepsia, they are not central to its definition.

Socioeconomic Impact of Nausea and Vomiting

Nausea and vomiting, from all causes, involve significant social and economic costs to affected patients, their employers, and the health care industry.[5–7] A recent analysis suggested that acute enteric infectious illnesses increase medical expenses by $1.25 billion and lead to $21.8 billion in lost productivity in the United States each year.[8] Two British studies reported that 8.5 million working days are lost each year because of the nausea of pregnancy and that severely affected patients miss a mean of 62 hours of work during their pregnancies.[9,10] Likewise, nausea and vomiting occurring after chemotherapy decrease employee productivity and further increase health care costs because of increased inpatient hospitalization and home nursing time.[5,6] Finally, it has been estimated that postoperative nausea and vomiting (PONV) incur additional costs of $415 per patient[10] at surgical centers and have a significant impact on the overall functioning of such centers.[13,14]

Differential Diagnosis of Nausea and Vomiting

The differential diagnosis of nausea and vomiting is extensive and includes a broad range of pathologic and physiologic conditions affecting the gastrointestinal tract, the peritoneal cavity, and the CNS as well as endocrine and metabolic functions (Table 2). Table 3 summarizes the anatomic locations, receptors involved, and specific therapeutic approaches for a variety of emetic stimuli.

Medications and Toxic Etiologies

Adverse medication reactions are among the most common causes of nausea and vomiting. In general, nausea in response to a drug is likely to present early in the course of its use. Thus, medications usually cause acute rather than chronic nausea and vomiting. Drug classes that induce nausea are varied and may have disparate sites of action. Medications that evoke vomiting by an action on the area postrema include dopaminergic agonists (such as L-dopa, bromocriptine), nicotine (including nicotine patches[15]), digoxin, and opiate analgesics. Nausea, for example, affects 40%–70% of cancer patients receiving narcotics for pain control. Other agents, such as nonsteroidal anti-inflammatory drugs and erythromycin, activate peripheral afferent pathways, most likely vagal, which then stimulate the brainstem nuclei that coordinate the act of vomiting. Other medications that may cause nausea and vomiting include cardiac antiarrhythmics, antihypertensives, diuretics, oral hypoglycemics, oral contraceptives, and gastrointestinal medications such as sulfasalazine.

The most extensively studied form of medication-related emesis is that provoked by cancer chemotherapeutic agents. Nausea and vomiting resulting from chemotherapy (postchemotherapy nausea and vomiting; PCNV) are classified as acute (within 24 hours), delayed ($\geq$1 day later), and anticipatory.

Table 2. Differential Diagnosis of Nausea and Vomiting

- **Medications and toxic etiologies**
  - Cancer chemotherapy
    - Severe—cisplatinum, dacarbazine, nitrogen mustard
    - Moderate—etoposide, methotrexate, cytarabine
    - Mild—fluorouracil, vinblastine, tamoxifen
  - Analgesics
    - Aspirin
    - Nonsteroidal anti-inflammatory drugs
    - Auranofin
    - Antigout drugs
  - Cardiovascular medications
    - Digoxin
    - Antiarrhythmics
    - Antihypertensives
    - β-Blockers
    - Calcium channel antagonists
  - Diuretics
  - Hormonal preparations/therapies
    - Oral antidiabetics
    - Oral contraceptives
  - Antibiotics/antivirals
    - Erythromycin
    - Tetracycline
    - Sulfonamides
    - Antituberculous drugs
    - Acyclovir
  - Gastrointestinal medications
    - Sulfasalazine
    - Azathioprine
  - Nicotine
    - CNS active
    - Narcotics
    - Antiparkinsonian drugs
    - Anticonvulsants
  - Antiasthmatics
    - Theophylline
  - Radiation therapy
  - Ethanol abuse
  - Jamaican vomiting sickness
  - Hypervitaminosis
- **Infectious causes**
  - Gastroenteritis
    - Viral
    - Bacterial
  - Nongastrointestinal infections
    - Otitis media
- **Disorders of the gut and peritoneum**
  - Mechanical obstruction
    - Gastric outlet obstruction
    - Small bowel obstruction
  - Functional gastrointestinal disorders
    - Gastroparesis
    - Chronic intestinal pseudo-obstruction
    - Nonulcer dyspepsia
    - Irritable bowel syndrome
  - Organic gastrointestinal disorders
    - Pancreatic adenocarcinoma
    - Inflammatory intraperitoneal disease
    - Peptic ulcer disease
    - Cholecystitis
    - Pancreatitis
    - Hepatitis
    - Crohn's disease
    - Mesenteric ischemia
    - Retroperitoneal fibrosis
    - Mucosal metastases
- **CNS causes**
  - Migraine
  - Increased intracranial pressure
    - Malignancy
    - Hemorrhage
    - Infarction
    - Abscess
    - Meningitis
    - Congenital malformation
    - Hydrocephalus
    - Pseudotumor cerebri
  - Seizure disorders
  - Demyelinating disorders
  - Emotional responses
  - Psychiatric disease
    - Psychogenic vomiting
    - Anxiety disorders
    - Depression
    - Pain
    - Anorexia nervosa
    - Bulimia nervosa
  - Labyrinthine disorders
    - Motion sickness
    - Labyrinthitis
    - Tumors
    - Meniere's disease
    - Iatrogenic
    - Fluorescein angiography
- **Endocrinologic and metabolic causes**
  - Pregnancy
  - Other endocrine and metabolic
    - Uremia
    - Diabetic ketoacidosis
    - Hyperparathyroidism
    - Hypoparathyroidism
    - Hyperthyroidism
    - Addison's disease
    - Acute intermittent porphyria
- **Postoperative nausea and vomiting**
- **Cyclic vomiting syndrome**
- **Miscellaneous causes**
  - Cardiac disease
    - Myocardial infarction
    - Congestive heart failure
    - Radiofrequency ablation
  - Starvation

Table 3. Anatomic Localization and Receptor Mediation of Clinical Emetic Stimuli in Humans

Anatomic site	Clinical stimuli	Receptors activated	Most common receptor-directed therapy
Area postrema	Medications (dopamine agonists, digoxin, opiates, nicotine, cytotoxics); metabolic (uremia, diabetic ketoacidosis, hypoxemia, hypercalcemia); bacterial toxins; radiation therapy	Dopamine D_2; serotonergic 5-HT_3; histaminergic H_1; muscarinic M_1; vasopressinergic	Antidopaminergics; ?5-HT_3 antagonists
Labyrinths	Motion sickness; labyrinthine tumors or infections; Meniere disease	Histaminergic H_1; muscarinic M_1	Antihistamines, anticholinergics
Peripheral afferents	Gastric irritants (copper sulfate, *Staphylococcus* enterotoxin, salicylate, antral distention); nongastric stimuli (colonic, biliary, or intestinal distention, peritonitis, mesenteric occlusion); chemotherapy; abdominal irradiation; pharyngeal stimulation	Serotonergic 5-HT_3	5-HT_3 antagonists
Cerebral cortex	Noxious odors, visions, or tastes	Poorly characterized	
Somatic pain			

Risk factors for acute chemotherapy-induced nausea include lower socioeconomic status, prechemotherapy nausea, female gender, administration of highly emetogenic chemotherapy, and absence of antiemetic therapy. In their analysis, Osoba et al.[16] documented a 20% prevalence of acute PCNV among those with none of those risk factors, compared with 76% in those with 4 or more. The occurrence of acute PCNV in an earlier treatment cycle is a potent predictor of its occurrence in subsequent cycles.[17] Based on a meta-analysis of 4 trials, Pater et al.[18] concluded that treatment factors (i.e., emetogenicity of chemotherapy regime and nature of antiemetic therapy) far outweighed patient or environmental factors in predicting PCNV. Acute vomiting is most likely to occur with cisplatinum, nitrogen mustard, and dacarbazine, all of which produce significant increases in plasma serotonin levels and/or urinary excretion of 5-hydroxyindole acetic acid (5-HIAA), a serotonin metabolite. Animal models show increases in ileal tissue levels of serotonin and increased numbers of serotonin-immunoreactive cells after cisplatinum administration.[19] Cisplatinum-evoked vomiting is reduced by vagotomy, suggesting its mediation by peripheral afferent neural pathways. However, the inability of the peripherally active 5-hydroxytryptamine$_3$ (HT_3)-receptor antagonist zatosetron-QUAT to block cisplatinum-induced emesis when given intravenously, coupled with a significant antiemetic effect when given intracerebroventricularly, indicates a central neural component to vomiting evoked by cisplatinum.[20] The acute nausea occurring after use of less emetogenic agents such as cyclophosphamide evokes little or no increase in plasma serotonin or urinary 5-HIAA levels. These findings are consistent with the clinical observations that 5-HT_3 antagonists are effective for preventing acute nausea from highly emetogenic agents but are less useful with symptoms produced by less nauseating chemotherapeutic drugs.

In contrast to acute chemotherapy-evoked vomiting, delayed and anticipatory vomiting are mediated by serotonin-independent pathways. Delayed emesis after cisplatinum administration, which may occur in up to 93% of patients,[21] is not associated with urinary 5-HIAA excretion and is not relieved by 5-HT_3–receptor antagonists. One investigation has shown increased norepinephrine production during delayed nausea from cisplatinum, suggesting the possibility of other neuroendocrine mediators.[22]

The principal risk factor for delayed PCNV is poor control of acute symptoms,[23] although age and tumor burden may also contribute.[24] In some patients, as many as 24% in one study, symptoms may be prolonged further, lasting longer than 2 weeks.[25] It has been suggested that gastroparesis may contribute to this phenomenon.[25,26] Anticipatory nausea and vomiting occur in 25%–50% of patients by the fourth course of cancer chemotherapy and are most prevalent among younger patients with underlying anxiety and especially among those who had adverse experiences in their last cycles of chemotherapy.[27,28]

Radiation therapy for malignancy can produce significant emesis by effects on both the structure and function of the gastrointestinal tract.[26,29–33] The incidence of nausea and vomiting is dependent on the location of the region irradiated and is as high as 80% when the upper abdomen is included in the radiation field.[33] Involvement of serotonergic pathways is indicated by the ability of 5-HT_3–receptor antagonists to reduce nausea and vomiting evoked acutely by abdominal radiation therapy.

Other ingested substances may produce prominent nausea and vomiting. Ethanol, when consumed in excess, evokes vomiting by a local action on the gastrointestinal tract and by central actions in the brainstem. Jamaican vomiting sickness occurs after eating unripe akee fruit. Excess intake of vitamin A also may cause nausea, vomiting, and hepatic injury.[34]

Infectious Causes

Gastrointestinal and systemic infections may produce nausea and vomiting, usually of acute onset. Acute enteric illness resulting in emesis is most prevalent in children younger than 3 years, then decreases in prevalence throughout childhood, only to become more common between ages 20 and 29 years. These illnesses occur at a rate of 1.2 infections per person per year and are most common in the autumn and winter. Viral gastroenteritis may be caused by the Hawaii agent, rotaviruses, reoviruses, and adenoviruses as well as the Snow Mountain and Norwalk agents. Bacterial infections with *Staphylococcus aureus*, *Salmonella*, *Bacillus cereus*, and *Clostridium perfringens* also produce nausea and vomiting, in many cases via toxins that act on the brainstem. The enterotoxin responsible for the emetic illness resulting from *S. aureus* has been characterized recently and is distinct from enterotoxins A–E and the toxic shock syndrome toxin 1.[35] Nausea in immunocompromised patients may be caused by gastrointestinal infection with cytomegalovirus or herpes simplex.[33,36] Nongastrointestinal infections associated with nausea include otitis media, meningitis, and hepatitis.

Disorders of the Gut and Peritoneal Cavity

Obstruction of the stomach or small intestine produces prominent nausea, which may be relieved by vomiting. Gastric outlet obstruction is often intermittent, whereas small intestinal obstruction usually is acute and associated with abdominal pain. Rarely, mesenteric ischemia may present as unexplained nausea and vomiting through the induction of ischemic gastroparesis.[37] Other rare causes of protracted nausea and vomiting include retroperitoneal fibrosis[38] and mucosal metastases.[39]

Functional disorders of gastrointestinal motility, such as gastroparesis, chronic intestinal pseudo-obstruction, and the Roux-en-Y syndrome,[40] produce nausea because of an inability to clear retained food and secretions. Gastroparesis may occur in relation to systemic diseases such as diabetes mellitus, scleroderma, systemic lupus erythematosus, polymyositis-dermatomyositis, and amyloidosis.[41] Delayed solid- or liquid-phase gastric emptying and electrogastrographic abnormalities[42] are prevalent in gastroesophageal reflux disease; however, symptoms correlate poorly with scintigraphic abnormalities.[43] Gastroparesis may also develop after vagotomy and gastric drainage operations or may be present in the absence of other disease[41] (idiopathic gastroparesis[44]). This condition may be preceded in some patients by prodromal symptoms such as diarrhea, fever, headache, or myalgias suggestive of viral etiology.[45,46] Occasionally, there may be more conclusive evidence of a viral etiology.[36,47] Nausea in pancreatic adenocarcinoma is associated with the development of gastroparesis; a paraneoplastic mechanism of inhibition of gastric motor function has been proposed.[48] The documentation of gastroparesis must not lead the clinician to assume that it is the fundamental cause of a given patient's symptoms; gastroparesis may be readily confused with gastric outlet obstruction, for example.[49]

Nausea and vomiting may be prominent symptoms in patients with functional dyspepsia. Delayed gastric emptying has been documented in 30%–82% of patients with functional dyspepsia, regardless of whether ulcer-like, reflux-like, or dysmotility-like symptoms predominate.[50] Other abnormalities identified among some with functional dyspepsia include gastric slow wave rhythm disturbances, abnormal partitioning of food within the stomach, impaired relaxation of the gastric fundus, and enhanced perception of gastric distention.[50] The relative importance of these phenomena and their role in symptom generation remain to be defined[50,51]; in some instances, they may be mere epiphenonema or occur secondary to primary central nervous or endocrine disorders.[33,50–53] Similarly, differentiation of "idiopathic" gastroparesis from functional dyspepsia, in general, remains arbitrary.

Abdominal disorders that do not directly involve the lumen of the gastrointestinal tract may also produce nausea and vomiting. Inflammatory conditions, such as pancreatitis, appendicitis, and cholecystitis, may activate afferent neural pathways arising from the peritoneum. Biliary colic, in the absence of inflammation, produces nausea via activation of afferents by distention of the biliary tree. Fulminant hepatic failure results in nausea, presumably caused by retention of as yet undefined emetic toxins and elevation of intracranial pressure.[54] Nausea and vomiting have also been reported in association with chemoembolization of hepatic tumors.[55]

CNS Causes

Any condition associated with increased intracranial pressure, be it tumor, infarction, hemorrhage, infection, or congenital disorder, may produce emesis, with or without concomitant nausea, via activation of brain stem

structures mediating vomiting. Focal lesions, especially those involving the brain stem and posterior fossa, may also cause and present as gastroparesis.[53,56,57] Studies in canine models show that the induction of emesis is maximal at an intracranial pressure of 80 mm Hg.[58] Nausea and vomiting may also be consequences of seizure disorders and are cardinal symptoms of migraine.[59–61] Rare examples of CNS disorders presenting as nausea and vomiting include brain stem demyelination,[62] neuroenteric cysts of the cerebellopontine angle,[63] and active neurocysticercosis lesions.[64]

Labyrinthine disorders produce nausea and vomiting, often with associated vertigo.[65] Motion sickness is induced by chronic repetitive movements, which stimulate afferent neural pathways that project to the vestibular nuclei and lead to activation of the brain stem nuclei, triggering the somatic and gastrointestinal aspects of emesis.[66] This activation is mediated primarily via histamine H_1 and muscarinic cholinergic rather than dopaminergic or serotonergic pathways; therefore, antihistamines and anticholinergics have assumed an important role in therapy.[67–69] Motion sickness is associated with extensive autonomic activation resulting in pallor, diaphoresis, and salivation.[66,68] Space sickness, experienced to varying degrees by most astronauts early in zero-gravity conditions, is related to motion sickness but may not include the associated autonomic phenomena.[70,71] Other labyrinthine causes of emesis include viral labyrinthitis, tumors, and Meniere's disease.[65]

Emotional responses to unpleasant smells or tastes can induce vomiting, as can unpleasant memories. Psychogenic vomiting occurs most commonly in young women, especially those with a history of psychiatric illness or social difficulties. Other psychiatric conditions associated with nausea include anxiety disorders, depression, anorexia nervosa, and bulimia nervosa.

Delayed gastric emptying and defects in antral motor and myoelectric dysfunction have been defined in many of these conditions; the pathogenetic significance of these findings is unclear.[41] In migraine, for example, vomiting of central origin is a common feature, yet this disorder has also been associated with gastroparesis.[53]

Endocrinologic and Metabolic Causes

Endocrinologic and metabolic causes of nausea and vomiting include uremia, diabetic ketoacidosis, hyperparathyroidism, hypoparathyroidism, hyperthyroidism, and Addison disease. The pathogenesis of symptoms in relation to these disorders is largely undefined; it is likely that multiple factors are involved. Activation of the area postrema has been postulated to occur in uremia, diabetic ketoacidosis, and hypercalcemia; a disruption of gastrointestinal motor activity may be more relevant to the pathogenesis of nausea and vomiting related to thyroid and parathyroid disease.

Pregnancy is the most common endocrinologic cause of emesis, which occurs in approximately 70% of women during the first trimester. On average, symptoms begin and end 39 days and 84 days after the last menses, respectively, and peak during the ninth week of gestation.[9,10,72,73] Nausea of pregnancy is more common among women who are primigravid, younger, less educated, overweight, and not employed outside the home. In general, first trimester vomiting is not deleterious to either the fetus or the mother and, in fact, has been reported to be associated with a reduced incidence of both miscarriage and fetal death. It has been suggested that the favorable pregnancy outcome reported with nausea and vomiting may be related to less use of tobacco and alcohol.[74] However, hyperemesis gravidarum, a condition of intractable vomiting that complicates between 1% and 5% of pregnancies, may result in dangerous fluid and electrolyte abnormalities.[72] The cause of nausea of pregnancy is uncertain, but it is likely to be hormonally related.[75] Although symptoms parallel the early increase in β-human chorionic gonadotrophin (β-HCG), the role of this hormone remains to be defined. For example, no reproducible differences in β-HCG release have been identified between those women who become nauseated and those who do not. There is a strong association between prior intolerance to oral contraceptives and subsequent first trimester nausea, suggesting potential roles for estrogen and progesterone.[73,74] Acute fatty liver of pregnancy can produce severe nausea and vomiting in the third trimester and can be complicated by liver failure, disseminated intravascular coagulation, and fetal and/or maternal death.

PONV

The prevalence of nausea and vomiting may complicate 11%–73% of surgical procedures.[12–14,76–78] One study of almost 4000 patients reported rates of 37% and 23% for nausea and vomiting, respectively, in patients undergoing general anesthesia.[79] Variations in reported prevalence are attributable to several factors. Postoperative nausea is more prevalent in women (risk 3 times that of men) and in younger patients (risk 2 times that of older patients).[80] Prevalence is also increased by the use of certain inhalation agents (nitrous oxide, in particular) and by concomitant use of opiate medications; the use of propofol as an intravenous anesthetic agent lowers the risk of PONV.[80] PONV is more likely to occur after general than regional anesthesia, and its prevalence increases in parallel with the duration of surgery and

anesthesia.[79–81] PONV is especially common after gynecologic and middle ear surgery and also occurs more commonly with abdominal and orthopedic surgery than with laparoscopic or other extra-abdominal operations.[78] PONV is also more likely in those with a history of PONV or motion sickness.[80,82]

Cyclic Vomiting

Cyclic vomiting, also referred to as "abdominal migraine" or "abdominal epilepsy," is a rare syndrome, characterized by discrete acute episodes of nausea and vomiting, separated by intervening asymptomatic periods, often associated with migraine headaches, motion sickness, and atopy. The mean age at onset is 5 years, and it demonstrates a female predominance.[83,84] Affected children typically experience 8 attacks per year, and the mean duration of each attack is 20 hours.[83–85] An association with mitochondrial DNA mutations has recently been described.[86] In a recent review of 225 children under 18 years of age who presented with the typical features of this syndrome, 121 were ultimately found to have an organic intra-abdominal, neurologic, endocrine, or metabolic cause.[83] Pfau et al.[84] emphasized the importance of the patients' history in differentiating cyclic vomiting from other causes of chronic vomiting in children; among 106 children with chronic vomiting, only 12% of those with a true cyclic pattern were found to have a gastrointestinal cause for their symptoms, in contrast to 76% of those with a more chronic pattern.[84] Cyclic vomiting has recently been reported among adults and has been postulated to result from disordered pituitary prostaglandin release.[87]

Miscellaneous Conditions

Nausea and vomiting may be prominent symptoms in acute myocardial infarction; although these symptoms were formerly regarded as being particularly common among those with inferior or posterior wall infarction, more recent studies suggest that the presence of nausea and vomiting correlates with infarct size rather than location.[88–90] Nausea may also occur in congestive heart failure, presumably from passive congestion of the liver and gut, and has been reported after radiofrequency catheter ablation for treatment of cardiac arrhythmias.[91] Prolonged starvation may lead to nausea and vomiting. Nausea and vomiting may also complicate fluorescein angiography.[92]

Functional Nausea and Vomiting

Functional nausea and vomiting is the term used to describe chronic unexplained symptoms.[93] In some situations, these symptoms may be associated with overt psychiatric features, and might therefore be classified as psychogenic; in others with vomiting, such manifestations are either absent or subtle.[93] The relationship of this patient group to those with functional dyspepsia and other related disorders is unclear, although the demonstration of a similar response to low-dose antidepressant therapy suggests a degree of demographic and/or pathophysiologic overlap.[93]

Clinical Approach to Nausea and Vomiting

Given the vast number and diversity of potential causes of nausea and vomiting, a carefully considered and orderly approach to the evaluation and treatment of patients with nausea and vomiting is needed to maintain cost effectiveness and avoid misdiagnosis (see Medical Position Statement). A comprehensive history and physical examination form the framework on which the diagnostic evaluation of these patients is based. A clear understanding of each patient's symptoms, and precisely what they mean by these symptoms, is crucial (Table 1).[94]

The acuteness of the symptomatology should be determined at the initial encounter. The nature of an acute illness can usually be detected on the basis of history and physical examination, supplemented where indicated by plain abdominal radiographs and appropriate blood tests. In this context, several issues need to be addressed. Is there an acute emergency, such as mechanical obstruction, perforation, or peritonitis? Does the patient need to be hospitalized for incapacitating symptoms, dehydration, and/or electrolyte abnormalities? Alternatively, can diagnostic tests, such as barium studies or endoscopy, be performed on an outpatient basis? Furthermore, are there clinical clues that the problem is likely to be self-limited, such as would be expected with viral gastroenteritis? Can a potentially offending medication be identified and discontinued? Should empiric treatment with an antiemetic, gastric acid–suppressing, or prokinetic agent be initiated?

The broad categories of clinical conditions that may cause these symptoms should be considered when a patient with chronic nausea and vomiting is evaluated. Symptom characteristics or the nature of associated symptoms often tend to incriminate one of these diagnostic categories. Medication-related toxicity and other iatrogenic causes can usually be identified by history alone. If symptoms suggest obstruction, radiographic studies should first be performed to exclude a mechanical cause. Partial or intermittent obstruction may at times be difficult to detect. Mucosal disorders of the stomach

and/or duodenum, such as peptic ulcer disease, may also cause chronic nausea and vomiting and are most accurately diagnosed by endoscopy. If neither obstruction nor mucosal disease is evident, systemic illness, CNS lesions, and psychologic factors should be considered. Finally, the possibility of an underlying motility disorder such as gastroparesis or small bowel dysmotility should be considered; if detected, an underlying cause should be sought.

On occasion, the cause of nausea and vomiting may remain undiagnosed after a careful initial evaluation. In some, the nature of the underlying disorder may begin to emerge over time and will become evident on subsequent reassessments.[95,96] In some, persistent symptoms may be psychogenic in origin[93] or attributable to the cyclic vomiting syndrome.[87,97] Although psychogenic vomiting is best illustrated by such disorders as anorexia nervosa or bulimia, it may also occur in relation to such conditions as panic disorders.

Initial Evaluation

History. Attention should be paid in the first instance to a clear definition of the clinical problem and to the differentiation of vomiting from regurgitation and rumination.

Symptom duration, frequency, and severity. Because the differential diagnosis of acute nausea and vomiting differs considerably from that of chronic nausea and vomiting, the definition of symptom duration is of paramount importance. Acute onset of nausea and vomiting suggests gastroenteritis, pancreatitis, cholecystitis, or a drug-related side effect. Most commonly, and particularly when nausea and vomiting are associated with diarrhea, headache, and myalgias, the cause is viral gastroenteritis; in this instance, symptoms should resolve spontaneously within 5 days. A more insidious onset of nausea, without vomiting, should raise suspicion of gastroparesis, a medication-related side effect, metabolic disorders, pregnancy, or even gastroesophageal reflux disease.[98] Nausea and vomiting are considered chronic when their duration is longer than 1 month.

Characteristics of vomiting episodes. The timing and description of the vomiting should be noted. Vomiting that occurs in the morning before breakfast is typical of that related to pregnancy, uremia, alcohol ingestion, and increased intracranial pressure. Intracranial disorders, especially those that result in increased intracranial pressure, are suggested by "projectile vomiting," although "ordinary" emesis may also occur.[99] Vomiting, in this circumstance, may not be preceded by nausea. Brainstem tumors frequently present with vomiting (30%–46%) and are usually accompanied by long tract or cranial nerve signs.[96]

The onset of vomiting caused by gastroparesis or gastric outlet obstruction tends to be delayed, usually by more than 1 hour, after meal ingestion.[99] Certain vomiting patterns may suggest specific psychiatric disorders. In anorexia nervosa or bulimia, vomiting typically occurs during or soon after a meal.[99] Continuous vomiting may be associated with a conversion disorder, and habitual postprandial or irregular vomiting is more typical of a major depression.[100] Patients with chronic psychogenic vomiting often report a history of organic or functional illness of the gastrointestinal tract. The original symptoms of "organic" origin are reinforced by the short-term benefits of initial therapy, and the now chronic symptoms represent a learned form of behavior.[100]

Details regarding the quality and quantity of the vomitus may also prove helpful. Regurgitation of undigested food is suggestive of such esophageal disorders as achalasia, esophageal stricture, or Zenker's diverticulum. Vomiting of partly digested food or chyme several hours after a meal suggests gastric outlet obstruction or gastroparesis, both of which often occur in the absence of significant pain. If the partially digested food is free of bile, gastric outlet obstruction is suggested; in contrast, bilious vomiting is characteristic of small bowel obstruction. A feculent or putrid odor to the vomitus, also a feature of intestinal obstruction, reflects bacterial degradation of stagnant intestinal contents.

Associated symptoms. Associated symptoms, such as abdominal pain, fever, diarrhea, vertigo, or a history of a similar contemporaneous illness among family and/or friends may guide the clinician toward the correct diagnosis.[101] A precise description of any associated pain may help to localize the underlying disease process, by suggesting the presence of a biliary or pancreatic disorder, for example. Abdominal pain preceding vomiting usually indicates an organic lesion, such as an obstruction.[94] With small bowel obstruction, pain is typically prominent, severe, and colicky and may temporarily improve after a vomiting episode.

Significant weight loss may indicate a malignant process; however, benign gastric outlet obstruction from ulcer disease may cause weight loss of similar degree by inducing sitophobia.

The presence of CNS symptoms such as headache, vertigo, neck stiffness, and focal neurologic deficits suggests a central cause of nausea and vomiting. The "classic" brain tumor headache—severe, worse in the morning, and associated with nausea and vomiting—occurs in

a minority of patients; very rarely, intractable vomiting is the sole manifestation of a brainstem tumor.[102] A history of intermittent episodes of vomiting, in association with a history of migraine, suggests the cyclic vomiting syndrome.[84]

Although complaints of early satiety and postprandial abdominal fullness/bloating and abdominal pain, in association with nausea and vomiting, may suggest underlying gastroparesis, these symptoms correlate poorly with results of gastric emptying studies.[43,50,103–106] In one recent study, for example, female gender, prominent symptoms of abdominal fullness/distention, and vomiting were the only historical features, among several evaluated, that proved predictive of gastroparesis in a large number of patients with dyspepsia.[103] This finding has led some to question the role of gastroparesis in symptom production in functional dyspepsia.[51]

Physical Examination

The physical examination is important for assessment of the consequences of nausea and vomiting and may help in determining the underlying condition. Signs of weight loss and dehydration should be sought. If the patient is not overtly hypotensive when supine, orthostatic vital signs should be obtained; a postural decrease in blood pressure and increase in pulse rate suggest significant dehydration; a decrease in blood pressure without any change in pulse rate suggests the presence of autonomic neuropathy.

The general examination will detect such important signs as jaundice, lymphadenopathy, abdominal masses, and occult blood in stool and may reveal features suggestive of thyrotoxicosis or Addison's disease.

The abdominal examination is of considerable importance. Emphasis should be placed on detection of distention, visible peristalsis, and abdominal or inguinal hernias. The definition of specific areas of tenderness is important: tenderness in the midepigastrium suggests an ulcer; in the right upper quadrant, cholecystitis or biliary tract disease. Listening over the epigastrium for a succussion splash on shaking the abdomen and pelvis or rapidly palpating the epigastrium will help identify gastric outlet obstruction or gastroparesis. Auscultation may demonstrate increased bowel sounds in obstruction or absent bowel sounds in ileus.

The extremities should be examined for changes suggesting scleroderma or peripheral neuropathy. Fingernails should be inspected for findings suggestive of self-induced vomiting. On inspection of the teeth, the discovery of loss of dental enamel may indicate either recurrent vomiting, as in bulimia, or the consequences of gastroesophageal reflux disease.

Neurologic examination unfortunately is often omitted in the evaluation of these patients. Crucial information may be readily obtained even by the nonneurologist if a number of simple maneuvers are performed: assessment of orthostatic hemodynamic changes, examination of the cranial nerves (including checking for nystagmus), fundoscopic examination, and observation of the patient's gait. Cranial nerve abnormalities and/or long tract signs suggest a central cause of the patient's symptoms.

Psychiatric causes, such as depression and anxiety, may also be recognized by the attentive physician during performance of the history and physical examination.

Blood Tests

The selection of laboratory studies and diagnostic tests should be directed primarily by the outcome of the history and physical examination.[94] The goals of such tests are (1) to assist in identifying the underlying cause and (2) to evaluate for consequences of vomiting. Basic laboratory testing includes a complete blood count and erythrocyte sedimentation rate together with electrolyte and standard chemistry profiles. In women, a pregnancy test is usually obtained, not only to define whether pregnancy might be the cause of symptoms, but also as a prerequisite to performing any radiologic studies. Further laboratory tests may include screening for abnormal thyroid function by estimating the serum level of thyroid-stimulating hormone. Serum drug levels may indicate toxicity among patients who are taking digoxin, theophylline, or salicylates. Severe and sustained vomiting, resulting in loss of water and electrolytes, may lead to dehydration and a hypokalemic metabolic alkalosis, caused in part by the loss of hydrochloric acid–containing gastric secretions. These laboratory tests may also provide the first clues to detection of other systemic disorders; for example, suspicion of Addison's disease will be aroused by the detection of hyponatremia. Further evaluation for metabolic disorders is indicated when screening results prove abnormal or when the patient history is compatible.[107]

Diagnostic Evaluation

The diagnostic evaluation should be directed first and foremost by the patient's history.[108] As testing proceeds, symptomatic treatment may be initiated on an empiric basis.[109] Some would go so far as to recommend a therapeutic trial as the initial approach in those without "alarm" symptoms. However, no controlled trials have confirmed the cost effectiveness of such an approach among patients whose primary presentation is nausea and vomiting. The relative costs, benefits, and risks of available diagnostic tests

Table 4. Relative Costs, Benefits, and Risks of Diagnostic Tests for Nausea and Vomiting

Test	Cost[a]	Benefit	Risk
Abdominal x-ray	$100	May suggest obstruction, CIIP; may be performed on day of clinical evaluation	Radiation exposure (minimal)
Upper GI barium study	$400	May reveal obstructive or mucosal lesions of upper GI tract	Radiation exposure (modest)
Upper GI and SBFT	$500	Examines small bowel, including terminal ileum	Radiation exposure (modest); may involve prolonged examination
Enteroclysis	$550	Optimal evaluation of small bowel mucosa	Radiation exposure (modest); oroduodenal intubation
Abdominal CT with oral and IV contrast	$900	Arguably the optimal technique to detect and diagnose cause of obstruction; also examines other intra-abdominal organs	Radiation exposure (modest); possible reaction to IV contrast
Gastric emptying scintigraphy	$600	Quantifies emptying rate of solids and/or liquids	Radiation exposure (minimal)
Esophagogastroduodenoscopy	$950	Optimal examination of esophageal, gastric and duodenal mucosa; biopsies possible	Minimal risk of bleeding, perforation, and sepsis; risks of sedation, if used
EGG	$150	May detect gastric dysrhythmias; indirect measure of gastric motility	None
Antroduodenal manometry	$900	Direct measure of intraluminal pressure changes; detects abnormal motor patterns	Radiation exposure (mild) if fluoroscopy used; nasal intubation

GI, gastrointestinal; IV, intravenous; CIIP, chronic idiopathic intestinal pseudo-obstruction.
[a]Estimated total cost.

are compared in Table 4. The approach to the diagnosis of mucosal or obstructive disease of the upper gastrointestinal tract is not reviewed in detail here; remarks are confined to a few specific comments. If the clinical presentation is in any way suggestive of mechanical obstruction, upright and supine abdominal radiographs should be obtained; they can be normal or show only nonspecific changes in 22% of patients with varying degrees of partial small bowel obstruction.[110,111] Although mucosal abnormalities (such as ulcers) or a proximal mechanical obstruction may be detected by either endoscopic or contrast radiologic studies,[112,113] standard esophagogastroduodenoscopy is both more sensitive and more specific for detection of mucosal lesions.[112,114–116] Double-contrast barium techniques have increased the sensitivity of radiologic studies[117]; the error rate, compared with endoscopy, is substantially lower than for single-contrast studies.[113,118,119] Radiologic studies in general are more readily available, are less expensive,[120] and are not associated with such rare sedation- and endoscopy-related complications as respiratory depression, perforation, and hemorrhage.[121–124] Two radiographic techniques are available to visualize the small intestine: the small bowel follow-through (SBFT) examination and the enteroclysis (or small bowel enema).[125] The SBFT is accurate in the presence of high-grade obstruction and usually provides an adequate assessment of the terminal ileum but may fail to detect low-grade obstruction and smaller mucosal lesions.[111,126,127] This has led some to advocate the enteroclysis study, which necessitates the placement of a nasoduodenal or oroduodenal tube directly into the small bowel; to achieve this, sedation using a benzodiazepine may occasionally be required.[128] Compared with SBFT, enteroclysis is more accurate in detecting small mucosal lesions[126,129] and mild to intermediate grades of small bowel obstruction and small bowel cancers.[111,130] However, small bowel tumors can be difficult to detect even with advanced radiologic studies.[131] Recent studies suggest that computed tomographic scanning, performed after administration of oral and intravenous contrast, may be the technique of choice for the detection and localization of intestinal obstruction. This modality has the additional advantage, in the context of the patient with unexplained nausea and vomiting, of identifying abdominal masses, as well as pancreatic, hepatobiliary, or retroperitoneal pathology.[132–136]

Tests of Gastric Motor Function

The most commonly used screening test of gastric motor function, relevant to this patient population, is the assessment of gastric emptying rate, usually performed using a meal labeled with a γ-emitting radionuclide.

Antroduodenal manometry and electrogastrography are performed only in a few tertiary referral centers.

Gastric emptying. Radioisotopic tests of gastric emptying offer a relatively easy, accurate, and noninvasive means to assess gastric motor function.[41,137] The patient ingests a radiolabeled meal, and its retention in or disappearance from the stomach is then monitored over time by serial images obtained using a γ camera placed over the upper abdomen. The radiation exposure from a standard solid-phase scintigraphic study of gastric emptying is approximately twice that incurred with an abdominal x-ray. Solid-phase meals are more sensitive than liquid-phase meals in detecting gastroparesis because normal emptying of liquids is often preserved until gastroparesis is advanced.[138] Breath tests and ultrasonography are being examined as alternatives to scintigraphy.[41,139]

The diagnosis of gastroparesis is typically based on the combination of compatible symptoms, delayed gastric emptying on scintigraphy, and the absence of obstruction and mucosal disease on endoscopic and/or radiologic evaluation of the upper gastrointestinal tract. An abnormal gastric emptying test result suggests but does not prove that symptoms are caused by gastroparesis; furthermore, emptying studies do not determine the cause of the gastroparesis.

Electrogastrography. Cutaneous electrogastrography (EGG) is performed by placing electrocardiography-type electrodes on the abdominal skin over the surface markings of the antrum and recording the frequency (normally approximately 3 cycles per minute) and regularity of gastric myoelectrical activity in the fasting state and for 60–120 minutes after a test meal.[140–142] Dysrhythmias are classified as rapid (tachygastria, >4 cycles/min) and slow (bradygastria, <2 cycles/min).[141] The amplitude of the signal provides a summation of gastric myoelectrical activity and correlates indirectly with gastric contractility. A reduction in or absence of the expected postprandial increase in the EGG amplitude, or power, has been shown to correlate with delayed gastric emptying and antral hypomotility.[143,144] Gastric dysrhythmias (both bradygastria and tachygastria) have been observed in patients with idiopathic[105,144–146] and diabetic[105,144,147] gastroparesis, nausea of pregnancy,[148] and motion sickness.[149] In addition, gastric dysrhythmias have been recorded on occasion in those with unexplained nausea and vomiting in the absence of altered gastric emptying.[94] Although correlations between gastric emptying and EGG results are far from perfect, it seems reasonable to state, based on limited available data, that abnormal EGG results, especially in the postprandial period, usually predict delayed gastric emptying.[144] Although some have suggested that gastric dysrhythmias may correlate better with symptoms than gastric emptying rate,[146] the place of this technique in the evaluation of these patients has not been defined.[137]

Antroduodenal manometry. Antroduodenal manometry involves the direct recording of intraluminal pressure changes (an indirect measurement of contractile activity) through perfusion ports or solid-state transducers incorporated in a catheter positioned under fluoroscopic guidance in the distal stomach and duodenum. Recordings may last from 5 hours (stationary study) to 24 hours (ambulatory study), are performed both in the fasting state and after meals,[41,137] and may be analyzed either by direct visual inspection or using a computer.[150] In the fasting state, the presence of the migrating motor complex and its site of initiation, direction of propagation, frequency, and duration are assessed.[137,151,152] After the meal, conversion to the fed state is identified, and the duration of the fed pattern is calculated.[137,153] Postprandial antral hypomotility is a common finding among those with unexplained nausea and vomiting and delayed gastric emptying,[137,154,155] and manometry has also been reported as useful in identifying those with primary or diffuse motor disorders.[155–158] However, the interpretation of antroduodenal manometric recordings requires substantial experience and a recognition of the considerable range of normal variation.[156,159,160] The specificity of many reportedly abnormal patterns has rarely been confirmed by correlation with histologic studies.[161]

It is only fair to mention that few data are available to guide the clinician in the appropriate performance of manometry in patients with unexplained nausea and vomiting; in one study, 42% had abnormal results, yet the manometric findings resulted in significant changes in therapy in only 13%.[162] What then is the role of manometry in the assessment of unexplained nausea and vomiting? If tests of gastric function reveal delayed emptying or abnormal myoelectrical activity, there is little added value in performing antroduodenal manometry, unless an awareness of small bowel dysfunction will alter treatment. When the gastric emptying or EGG results are normal or equivocal and severe symptoms persist despite empiric therapeutic trials, antroduodenal manometry may be indicated.[108] Occasionally, findings consistent with chronic intestinal pseudo-obstruction may be revealed[163] or features consistent with mechanical obstruction identified in patients in whom they had not

been detected radiographically.[164] Others have emphasized the value of a normal result: by demonstration of normal motor function in the antrum and the duodenum, any lingering questions regarding dysmotility can be resolved and the diagnostic evaluation redirected elsewhere.[165]

Abdominal Imaging

In addition to the aforementioned role of computed tomography scanning, ultrasonography may also provide valuable information if gallbladder, pancreatic, or hepatobiliary pathology is suspected.

Evaluation for Central Disorders

Although much feared, it is rare for an adult patient with vomiting related to an intracranial mass not to have either neurologic symptoms, most commonly headache, or neurologic signs, such as cranial nerve findings, long tract signs, or papilledema.[95,166] Because objective neurologic findings may occasionally be absent in patients with intracranial lesions, an imaging study should be considered in those with severe, unexplained chronic nausea and vomiting[102]; magnetic resonance imaging, by virtue of superior visualization of the posterior fossa, is now considered the study of choice in this situation.[167]

Evaluation for Psychogenic Causes

In patients with chronic unexplained nausea and vomiting, psychologic assessment may be of benefit. Once common organic causes and gastrointestinal dysmotility have been excluded, psychogenic vomiting should enter the differential diagnosis. A definitive diagnosis of psychogenic vomiting may be especially difficult to make but may be aided by recourse to a number of instruments designed to detect significant psychologic contributions to functional symptoms. On the Minnesota Multiphasic Personality Inventory and other instruments, elevated scores for hypochondriasis, depression, and hysteria have been demonstrated among patients with nausea of presumed psychogenic origin.[168]

Management of Nausea and Vomiting

General principles

Treatment of the patient with nausea and vomiting must address a number of important issues.[94] These include (1) correction of any fluid, electrolyte, or nutritional deficiencies that may have resulted from vomiting itself or the food aversion that may accompany these symptoms; (2) identification and elimination of the underlying cause of the symptoms where possible; and (3) suppression or elimination of the symptoms themselves if the primary cause cannot be identified easily and promptly eliminated.

In the patient with either acute or chronic vomiting, dehydration and malnutrition may be caused by cessation of oral intake of fluid, electrolytes, and nutrients and by direct loss of fluid and electrolytes in the vomitus. In a normal individual, the salivary glands and the stomach each secrete 1–2 L of fluid per day—these secretions contain sodium, hydrochloric acid, and potassium; if vomiting is protracted, dehydration, hypokalemia, and metabolic alkalosis will result. Hypokalemia will be exacerbated by the exchange of sodium for potassium in the renal tubule in an attempt to conserve sodium losses. Contraction of extracellular fluid, bicarbonate losses, and shifts of hydrogen into the cells as a further consequence of potassium deficiency also contribute to alkalosis. Therefore, a primary goal of treatment of the patient with protracted vomiting is careful assessment of fluid and electrolyte status followed by appropriate replacement. Fluid replacement should be based on the administration of normal saline solutions with appropriate potassium supplementation. If it becomes clinically necessary to place a nasogastric tube to relieve gastric distention, for example, the output from the nasogastric tube should be measured on a regular basis and appropriate replacement performed. In some circumstances, such as in the patient with nausea and vomiting related to gastroparesis, dietary measures may be of considerable importance[104]; strategies may include consumption of frequent small meals, reduction of the fat content of meals, avoidance of indigestible or partially digestible material (to prevent bezoar formation), and elimination of carbonated beverages to reduce gastric distention. If necessary, the diet may be further modified by use of a blender or, in more extreme circumstances, by provision of all calories in the form of liquid formulas.

Pharmacologic Approaches

A major limitation of the available literature on pharmacologic treatment of nausea and vomiting is the striking paucity of controlled trials of therapies for the most common causes of these symptoms. This may relate in part to the fact that nausea and vomiting in many of these circumstances are short-lived and resolve spontaneously. Most clinical trials have been performed in circumstances associated with a high risk of nausea and vomiting—surgery, intensive chemotherapy, and radiation therapy. Although these may provide useful information on the relative efficacy of various agents, it may not be appropriate to extrapolate results to other clinical

situations. One important theme that emerges from the literature is the difference in therapeutic response between nausea and vomiting; the former is often more resistant to pharmacologic interventions, both prophylactic and therapeutic. This may relate to the differences in the physiology of these symptoms.

Two broad categories of agents are used: antiemetics and prokinetics. Antiemetics act primarily within the CNS to suppress nausea and prevent vomiting (Table 5). The principal classes of drugs that have been used for symptomatic treatment of nausea and vomiting are phenothiazines, antihistamines, anticholinergics, dopamine antagonists, and serotonin antagonists. Other classes of compounds that have been shown to have antiemetic properties are butyrophenones, cannabinoids, other substituted benzamides, steroids, and benzodiazapines.

Antiemetic Agents

Although a variety of anticholinergic agents have been shown to have antiemetic effects, their clinical utility has been limited by relatively modest efficacy and poor tolerance because of the frequency of other anticholinergic side effects. Currently, the only anticholinergic agent that enjoys any degree of use is scopolamine, administered as a transdermal patch. It is used principally for prophylaxis and treatment of motion sickness; more selective antimuscarinic agents, such as zamifenacin (an M_3-, M_5-receptor antagonist), appear equally effective.[169,170] Scopolamine has been shown to have mild efficacy against cytotoxic chemotherapy-related nausea and vomiting and may have a role as adjunctive therapy in this context.

Antihistamine drugs with histamine H_1-receptor antagonistic properties have central antiemetic effects. Agents such as meclizine and diphenhydramine are available both over the counter and by prescription for symptomatic therapy of nausea and vomiting. Disorders such as motion sickness, vertigo, and migraine, in which nausea and vomiting are of labyrinthine origin, are managed primarily by histamine H_1- and cholinergic muscarinic M_1-receptor antagonists. In clinical studies, dimenhydrinate, dramamine, cyclizine, cinnarizine, marezine, scopolamine, and meclizine, among others, have shown efficacy in the prevention and treatment of motion sickness.[169–172] These agents induce variable degrees of drowsiness.

Phenothiazine compounds have long been recognized as possessing significant antiemetic properties. Their actions appear to be mediated primarily through a central antidopaminergic mechanism in the area postrema. Commonly used agents in this class include prochlorperazine, promethazine, chlorpromazine, thiethylperazine, and perphenazine. These compounds are variably available in tablet or capsule form, as suspensions, as suppositories, and for injectable use and are commonly used for more severe episodes of nausea and vomiting, including those related to vertigo,[65] motion sickness,[66,173–176] and migraine.[59,60,177] Of this group, prochlorperazine is perhaps one of the most widely used agents for the treatment of moderate to severe nausea and vomiting and has demonstrated efficacy in PONV and PCNV.[178] Its availability in formulations suitable for oral, rectal, and parenteral use provides considerable flexibility, particularly for the patient who is unable to tolerate orally administered compounds. Side effects of these compounds are relatively frequent and include sedation, orthostatic hypotension, and extrapyramidal symptoms, including dystonia and tardive dyskinesia. Rarely, other phenothiazine-type idiosyncratic reactions, such as the neuroleptic malignant syndrome, blood dyscrasias, and cholestatic jaundice, have also been reported.

Table 5. Antiemetic Agents

	Oral			
	Caps/tabs	Syrup	Suppository	Parenteral
Anticholinergics				
Scopolamine[a]	−	−	−	−
Antihistamines				
Meclizine	+	+	−	
Diphenhydramine	+	+	−	−
Cinnarizine	+	−	−	−
Cyclizine	+	+	−	+
Hydroxyzine	+	+	−	+
Phenothiazines				
Prochlorperazine	+	+	+	+
Promethazine	+	+	+	+
Chlorpromazine	+	+	+	+
Thiethylperazine	+			+
Perphenazine	+			+
Benzamides				
Benzoquinamide	−	−	−	+
Trimethobenzamide	+	+	+	+
Metoclopramide	+	+	−	+
Domperidone	+	−	−	−
5-HT_3 antagonists				
Ondansetron	+	−	−	+
Granisetron	+	−	−	+
Cannabinoids				
Dronabinol	+	−	−	−
Nabilone	+	−	−	−
Benzodiazepines				
Lorazepam	+	−	−	+
Alprazolam	+	−	−	−
Corticosteroids				
Dexamethasone	−	−	−	+
Methylprednisolone	−	−	−	+
Butyrophenones				
Droperidol	−	−	−	+

[a]Available in transdermal form.

The butyrophenones, haloperidol and droperidol, also probably act via a central antidopaminergic effect.[179] Droperidol, in particular, has been shown to be useful in the treatment of anticipatory and acute chemotherapy-related nausea and vomiting, and also in the therapy of PONV. Side effects include sedation, agitation, and restlessness.

Serotonin (5-HT) antagonists have recently been added to the list of clinically effective antiemetic agents.[180] A particular advance has been the development of a number of relatively specific 5-HT_3 antagonists, including ondansetron, granisetron, tropisetron, and dolasetron. They may well operate at both central and peripheral locations. Given that the highest density of 5-HT_3 receptors is in the area postrema, it is thought that the primary site of action of these compounds is on the chemoreceptor trigger zone.[181] They are well tolerated, and side effects such as gastrointestinal upset and headache appear to be relatively uncommon.

Domperidone[182] and metoclopramide[183] are substituted benzamides that act primarily as dopamine antagonists and appear to have both central and peripheral actions. They also appear to have some direct and indirect cholinergic effects. Both agents are distinctive in that they exert both antiemetic and prokinetic effects. They are differentiated by the fact that domperidone penetrates the blood–brain barrier poorly, so although it has effects on the chemoreceptor trigger zone, which is on the blood side of the barrier, it does not enter the CNS to any significant extent and is therefore free of the centrally mediated extrapyramidal side effects that are relatively common with metoclopramide. Both have been shown to be moderately effective in the treatment of nausea and vomiting and have been used in a variety of clinical contexts. Domperidone is not yet available for use in the United States, but metoclopramide is available for oral and parenteral use—an advantage in the patient with severe episodes of central vomiting.[59,60,65] Both have been shown to exert prokinetic effects on the esophagus, stomach, and upper small intestine and thus have been used in the treatment of gastroesophageal reflux and gastroparesis in particular. Because of their dual action as prokinetics and antiemetics, they may be particularly useful in the patient with nausea and vomiting related to gastroparesis such as diabetic gastroenteropathy. Because of the relative rarity of extrapyramidal effects with domperidone, it has also proved useful in the therapy of nausea and vomiting related to dopaminergic agents used in the treatment of Parkinson's disease.[184] In the treatment of acute chemotherapy-related nausea and vomiting, metoclopramide has been found to be inferior to ondansetron; however, there is some suggestion that domperidone may be superior to serotonin antagonists for delayed PCNV.

A major limiting factor in the use of metoclopramide is the relative frequency of significant adverse effects. Adverse effects appear to be particularly common in young children and the elderly and include fatigue and such extrapyramidal phenomena as dystonia, dyskinesia, akathisia, opisthotonos, and oculogyric crises. Metoclopramide also induces hyperprolactinemia, which may result in gynecomastia and galactorrhea. The overall incidence of adverse effects with metoclopramide is 10%–20%. The overall frequency of side effects with domperidone appears to be in the region of 5%–10%; extrapyramidal effects are distinctly uncommon, but hyperprolactinemia-related effects and headaches do occur. Other agents classified as substituted benzamides that also have antiemetic effects are benzoquimanide, trimethobenzamide, and alizapride. These have been used in the treatment of moderate to severe nausea and vomiting in a variety of clinical contexts.

Anecdotal reports led to the investigation of cannabinoids in the treatment of nausea and vomiting. These agents appear to act centrally in the region of the medulla oblongata. Of this class of compounds, dronabinol is available for use in the United States and is indicated for anorexia resulting in weight loss among patients with the acquired immunodeficiency syndrome and for refractory chemotherapy-related nausea and vomiting.[178] Side effects include sedation, hypotension, ataxia, dizziness, and euphoria.

A variety of other agents have been used for the treatment of severe chemotherapy-related nausea and vomiting in particular. Corticosteroids, especially dexamethasone, have been used primarily in combination with other agents such as metoclopramide and ondansetron in the treatment of chemotherapy-related nausea and vomiting, acting perhaps by reducing prostaglandin formation. Benzodiazepines such as lorazepam and diazepam have also been shown to be effective as adjunctive agents in the treatment of cytotoxic chemotherapy-related nausea and vomiting.

The latest class of compounds to show efficacy as antiemetics are the neurokinin-1 antagonists, which in preliminary studies have shown impressive efficacy in both acute and delayed PCNV.[185]

Prokinetic Agents

Prokinetic agents are used primarily in gastroesophageal reflux disease, gastroparesis, and other putative dysmotility syndromes. A number of common

themes emerge from a review of the pharmacology of motility.[186] Given the ubiquity of many of these receptors in various neuronal systems, it is not surprising that the usefulness of several prokinetic agents has been limited by CNS and cardiovascular side effects. With many agents, tolerance has been a problem, and long-term efficacy often proves elusive.

Cholinergic agonists are the original promotility agents and were relied upon for their effect primarily on stimulation of muscarinic M_2-type receptors on the smooth muscle cell. Evidence of their effectiveness in motility disorders is generally inconsistent, although benefits in reflux disease and gastroparesis have been claimed.[187] Not surprisingly, given their nonspecificity, they are associated with a significant incidence of adverse effects, and their use has virtually disappeared with the advent of newer agents.

Dopamine antagonists also act as prokinetics; several studies have demonstrated some efficacy for metoclopramide in gastroesophageal reflux disease and gastroparesis.[187,188] Domperidone has demonstrated efficacy in gastroparesis and functional dyspepsia.[182] Other agents that have some dopamine antagonist effects include clebopride, cinitapride, and perhaps cisapride. Metoclopramide and clebopride may also potentiate acetylcholine release.

Cisapride, a substitute benzamide, has been the focus of several experimental and clinical studies.[189] Its mode of action involves the facilitation of acetylcholine release from myenteric neurons[190] through a 5-HT_4 receptor–mediated effect. Among oral prokinetic agents (metoclopramide, domperidone, erythromycin, and cisapride), cisapride appears to have the most diffuse gastrointestinal effects. It also appeared to benefit from an apparently low incidence of adverse effects; neurologic and hormonal abnormalities are distinctly unusual, and mild diarrhea and abdominal cramping are the only problems consistently associated with its use. Recently, however, concern was raised after reports of a proarrhythmic effect of cisapride, usually occurring in the context of cotherapy with other agents that impair cisapride metabolism or prolong the Q–T interval.[191] This concern led to withdrawal of cisapride in the United States and elsewhere and to extensive warnings and requirement of pretherapy electrocardiograms in many other countries. With regard to the development of tolerance on long-term therapy, the status of cisapride remains somewhat uncertain, although studies to date suggest that this may be less of a problem than with metoclopramide and domperidone. Some studies have certainly shown continuing efficacy for up to 1 year in gastroparesis.[192] Several studies have demonstrated benefits with cisapride in gastroparesis and pseudo-obstruction.[193–196] In both short- and long-term studies, the Mayo clinic group demonstrated improvements in gastric emptying and motility in patients with gastroparesis and chronic intestinal pseudo-obstruction.[192,196] However, the relationship between objective improvements in emptying and symptom relief was somewhat inconsistent. Recently, Camilleri et al.[197] suggested that aspects of autonomic function may influence the response to cisapride.

Although it has been recognized for some time that erythromycin, a macrolide, is associated with significant gastrointestinal effects, the possibility that these are related to the stimulation of motility was not recognized until recently. It is now clear that erythromycin exerts a dose-dependent stimulatory effect on foregut motility[198] and inhibits isolated pyloric pressure waves and pyloric tone.[199] These direct effects on contractile activity translate into acceleration of gastric emptying, abolition of the lag phase of solid emptying, emptying of nondigestible solids, and the induction of "dumping."[200–205] Although several studies have consistently demonstrated the efficacy of intravenous erythromycin, the efficacy of oral administration is more controversial. Thus, not all studies have demonstrated long-term benefits in such conditions as gastroparesis, postvagotomy gastric stasis, the roux syndrome, and intestinal pseudo-obstruction.[206] In a recent comprehensive interview, Camilleri[206] concluded that erythromycin was most useful in acute situations and recommended a regimen that began with intravenous erythromycin (3 mg/kg every 8 hours) and continued with oral administration (250 mg 3 times a day) for 5–7 days. Current research seeks to develop a macrolide, devoid of antibiotic activity, that has more predictable efficacy when administered by mouth and is associated with a lower incidence of adverse effects than erythromycin.

Specific Clinical Situations

Intractable Nausea and Vomiting Related to Gastroparesis

Surgical treatment of gastroparesis and motility disorders has proven disappointing in general, and the temptation to proceed to bypass procedures should be particularly resisted. Results of resection in patients with diabetic gastroparesis have also been disappointing. However, for patients with postoperative gastroparesis in whom medical management has failed, resection may be considered. If resection is performed, a subtotal gastrectomy, rather than less extensive resections, appears to give the best results.

Endoscopic placement of a percutaneous endoscopic gastrostomy (PEG) may provide the patient who has prominent distention with relief when symptoms are distressing. Recently, two pilot studies have suggested that gastric pacing may dramatically relieve symptoms among patients with intractable nausea and vomiting related to gastroparesis.[207,208]

PONV

In PONV, the focus has been on prevention rather than therapy; of 75 randomized trials and 4 meta-analyses reviewed, only 8 trials and 1 meta-analysis addressed the management of established nausea and vomiting. Furthermore, few attempts have been made to address the overall efficacy of a prophylactic strategy. In their assessment, Tramer et al.[209] suggest that although prophylaxis with ondansetron (one of the more effective agents in comparative trials) was slightly more effective than treatment of PONV when it developed, it was less cost-effective and associated with more adverse effects. From trials of prophylaxis, certain themes emerge. Nausea is more difficult to prevent than vomiting, and the omission of nitrous oxide[210] and inclusion of propofol in induction and maintenance of anesthesia[80,211,212] will reduce the prevalence of PONV. Of the multitude of pharmacologic agents tested, the 5-HT_3 antagonists and droperidol have proven most effective in comparisons both with placebo and with other agents in large randomized trials.[213–224] Comparisons between various 5-HT_3 antagonists or between members of this class of compounds and droperidol have generally found similar efficacies for all.[213,216,218,222–224] Tramer et al.[225] performed an important meta-analysis of 53 trials involving 7177 patients who had received 24 different ondansetron regimens and 5712 control subjects. These subjects were at high risk for PONV, as indicated by average early and late incidences of PONV of 40% and 60%, respectively, among those who received no therapy or placebo. They concluded that with an optimal regimen (8 mg intravenously, 16 mg orally), the best number needed to treat to prevent PONV in a high-risk group was between 5 and 6. Major adverse effects were headache and abnormal liver enzyme levels.[225] 5-HT_3 antagonists are also effective in the treatment of established PONV; intravenous doses of ondansetron ranging from 1 to 8 mg have a response rate that is, on average, 25% higher than that of placebo.[226] Other studies show similar efficacy for granisetron[227] and tropisetron.[228]

Chemotherapy- and Radiation-Related Nausea and Vomiting

For the prevention of acute PCNV, the combination of a 5-HT_3 antagonist and dexamethasone is now the preferred option.[229–236] In a meta-analysis, addition of dexamethasone to a 5-HT_3 antagonist increased the complete control rate from 39%–79% to 58%–92%.[230] The various 5-HT_3 antagonists appear to be of similar efficacy and have a comparable incidence of side effects.[231,234,235,237] Doses used in this context are considerably higher than in other circumstances.[231,235,237,238] Cocktails containing high-dose metoclopramide (2 mg/kg intravenously), dexamethasone, antihistamines, and benzodiazepines have also been shown to be effective in prevention and treatment of PCNV but have largely been replaced by regimens that incorporate a 5-HT_3 antagonist. 5-HT_3 antagonists, either alone or in combination with corticosteroids, appear to be less effective in the prevention and treatment of delayed PCNV.[23,233,239–245] For this situation, a combination of dexamethasone and metoclopramide is recommended[236]; however, even this regime still has a failure rate of approximately 40%. There is some evidence of efficacy for benzodiazepines and substituted benzamides.[242,246] Most exciting, in this context, is the recent report of the efficacy of a neurokinin-1–receptor antagonist in the prevention of PCNV. The addition of this oral agent to a combination of granisetron (10 μg/kg) and dexamethasone (20 mg) not only increased the complete control rate for acute emesis from 67% to 93% but demonstrated a complete control rate of 80% for delayed vomiting—a rate not achieved previously by other regimens.[185] Few studies have addressed the prevention and treatment of anticipatory PCNV; available evidence suggests that in the prevention and control of acute and delayed PCNV, benzodiazepines and relaxation therapy may have some efficacy.[247,248]

5-HT_3 antagonists have also been shown to be more effective than either placebo or other agents such as chlorpromazine, dexamethasone, and prochlorperazine in the prevention of radiotherapy-induced nausea and vomiting,[249–252] as well as in the treatment of nausea and vomiting that is unrelated to chemotherapy and radiation therapy in cancer patients.[253]

Morning Sickness and Hyperemesis Gravidarum

Prevention and treatment of morning sickness and hyperemesis gravidarum are complicated by a gen-

eral reluctance to use pharmacologic agents in pregnant patients. Debendox, formerly a widely used preparation for the treatment of these symptoms, was withdrawn because of possible teratogenic effects, and the development of therapeutic agents in this area was significantly compromised by the unfortunate consequences of the use of thalidomide in Europe. Conventionally, antiemetics are not prescribed before 12 weeks' gestation.[254,255] Because of its relative safety, pyridoxine has been advocated, although evidence of its antiemetic efficacy is lacking. For more severe symptoms and for hyperemesis, hospitalization, fluid and electrolyte replacement, thiamine supplementation, and administration of antiemetics including antihistamines, such as meclizine, and phenothiazines, such as promethazine, may be used.[254,255] Alternative therapies such as acupressure[256,257] have also been effective. For more severe cases of hyperemesis gravidarum, parenteral prochlorperazine, chlorpromazine, and metoclopramide have been used. Only 4 randomized trials of any therapy for hyperemesis gravidarum have been conducted. Although adrenocorticotropin proved no better than placebo,[258] a recent trial suggested that oral methylprednisolone was superior to promethazine.[259] Although the failure rate was similar with both therapies, those who received the steroid therapy had a shorter duration of vomiting and were far less likely to experience an early relapse.[259] Other studies have suggested efficacy for ginger[260] but no advantage for ondansetron over promethazine.[261] For those with hyperemesis gravidarum that is resistant to those interventions, total parenteral or enteral nutrition may be necessary.[262]

EAMONN M. M. QUIGLEY
Sections of Gastroenterology and Hepatology
University of Nebraska Medical Center
Omaha, Nebraska
Department of Medicine
National University of Ireland
Cork, Ireland

WILIAM L. HASLER
University of Michigan Health Sciences Center
Ann Arbor, Michigan

HENRY P. PARKMAN
Temple University School of Medicine
Philadelphia, Pennsylvania

References

1. Talley NJ, Silverstein MD, Agreus L, Nyren O, Sonnenberg A, Holtmann G. AGA technical review: evaluation of dyspepsia. Gastroenterology 1998;114:582–595.
2. Amarnath RP, Abell TL, Malagelada JR. The rumination syndrome in adults. Ann Intern Med 1986;105:513–518.
3. O'Brien MD, Bruce BK, Camilleri M. The rumination syndrome: clinical features rather than manometric diagnosis. Gastroenterology 1995;108:1024–1029.
4. Soykan I, Chen J, Kendall BJ, McCallum RW. The rumination syndrome: clinical and manometric profile, therapy and long-term outcome. Dig Dis Sci 1997;42:1866–1872.
5. Rusthoven JJ, Osoba D, Butts CA, Yelle L, Findlay H, Grenville A. The impact of post chemotherapy nausea and vomiting on quality of life after moderately emetogenic chemotherapy. Support Care Cancer 1998;6:389–395.
6. Grunberg SM, Boutin N, Ireland A, Miner S, Silveria J, Ashikaga T. Impact of nausea/vomiting on quality of life as a visual analogue scale–derived utility score. Support Care Cancer 1996;4:435–439.
7. Farup C, Leidy NK, Murray M, Williams R, Helbers L, Quigley EMM. The effect of domperidone on the health-related quality of life of patients with diabetic gastropathy. Diabetes Care 1998; 21:1699–1706.
8. Garthright WE, Archer DL, Kvenberg JE. Estimates of incidence and costs of intestinal infectious diseases in the United States. Public Health Rep 1988;103:107–115.
9. Gadsby R. Pregnancy sickness and symptoms: your questions answered. Prof Care Mother Child 1994;4:16–17.
10. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993; 43:245-248.
11. Osoba D, Zee B, Warr D, Latreille J, Kaizer L, Pater J. Effect of postchemotherapy nausea and vomiting on health-related quality of life. The Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. Support Care Cancer 1997;5:307–313.
12. Carroll NV, Miederhoff PA, Cox FM, Hirsch JD. Costs incurred by outpatient surgical centers in managing postoperative nausea and vomiting. J Clin Anesth 1994;6:364–369.
13. Hirsch J. Impact of postoperative nausea and vomiting in the surgical setting. Anaesthesia 1994;49(suppl):30–33.
14. Westman HR. Post-operative complications and unanticipated hospital admissions. Semin Pediatr Surg 1999;8:23–29.
15. Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Safety 1998;18:297–308.
16. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L. Determinants of postchemotherapy nausea and vomiting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1997;15:116–123.
17. Morrow GR, Roscoe JA, Hickok JT, Stern RM, Pierce HI, King DB, Banerjee TK, Weiden P. Initial control of chemotherapy-induced nausea and vomiting in patient quality of life. Oncology 1998; 12:32–37.
18. Pater J, Slamet L, Zee B, Osoba D, Warr D, Rusthoven J. Inconsistency of prognostic factors for post-chemotherapy nausea and vomiting. Support Care Cancer 1994;2:161–166.
19. Fukui H, Yamamoto M, Ando T, Sasaki S, Sato S. Increase in serotonin levels in the dog ileum and blood by cisplatin as measured by microdialysis. Neuropharmacology 1993;32:959–968.
20. Gidda JS, Evans DC, Cohen ML, Wong DT, Robertson DW, Parli CJ. Antagonism of serotonin$_3$ (5-HT$_3$) receptors within the blood-brain barrier prevents cisplatin-induced emesis in dogs. J Pharmacol Exp Ther 1995;273:695–701.
21. Kris MG, Gralla RJ, Clark RA, Tyson LB, O'Connell JP, Wertheim MS, Kelsen DP. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. J Clin Oncol 1985;3:1379–1384.
22. Fredrikson M, Hursti TJ, Steineck G, Furst CJ, Borjesson S, Peterson C. Delayed chemotherapy-induced nausea is aug-

mented by high levels of endogenous noradrenaline. Br J Cancer 1994;70:642–645.
23. Goedhals L, Heron JF, Kleisbauer JP, Pagani O, Sessa C. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: a double-blind, placebo-controlled, comparative study. Ann Oncol 1998;9:661–666.
24. Hursti TJ, Avall-Lundqvist E, Borjeson S, Fredrikson M, Furst CJ, Steineck G, Peterson C. Impact of tumour burden on chemotherapy-induced nausea and vomiting. Br J Cancer 1996;74: 1114–1119.
25. Hecht JR, Lembo T, Chap L. Prolonged nausea and vomiting after high dose chemotherapy and autologous peripheral stem cell transplantation in the treatment of high risk breast carcinoma. Cancer 1997;79:1698–1702.
26. Brand RE, Di Biase JK, Quigley EMM, Gobar LS, Harmon KS, Lynch JC, Bierman PJ, Bishop MR, Tarantolo SR. Gastroparesis as a cause of nausea and vomiting after high-dose chemotherapy and haemopoietic stem-cell transplantation. Lancet 1998; 352:1985.
27. Watson M, Meyer L, Thomson A, Osofsky S. Psychological factors predicting nausea and vomiting in breast cancer patients on chemotherapy. Eur J Cancer 1998;34:831–837.
28. Morrow GR. Clinical characteristics associated with the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment. J Clin Oncol 1984;2:1170–1176.
29. Sturm A, Van Der Ohe M, Rosien U, Goebell H, Layer P. Treatment of radiotherapy-induced gastroparesis with erythromycin. Deutsche Med Wochenschr 1996;121:402–405.
30. Otterson MF, Sarna SK, Moulder JE. Effects of fractionated doses of ionizing radiation on small intestinal motor activity. Gastroenterology 1988;95:1249–1257.
31. Otterson MF, Sarna SK, Lee MB. Fractionated doses of ionizing radiation alter postprandial small intestinal motor activity. Dig Dis Sci 1992;37:709–715.
32. Erickson BA, Otterson MF, Moulder JE, Sarna SK. Altered motility causes the early gastrointestinal toxicity of irradiation. Int J Radiat Oncol Biol Phys 1994;28:905–912.
33. DiBiase JK, Quigley EMM. Tumor related dysmotility. Gastrointestinal dysmotility syndromes associated with tumors. Dig Dis Sci 1998;43:1369–1401.
34. Leo MA, Lieber CS. Hypervitaminosis A: a liver lover's lament. Hepatology 1988;8:412–417.
35. Su YC, Wong AC. Identification and purification of a new staphylococcal enterotoxin, H. Appl Environ Microbiol 1995; 61:1438–1443.
36. Nowak TV, Goddard M, Batteiger B, Cummings OW. Evolution of acute cytomegalovirus gastritis to chronic gastrointestinal dysmotility in a non-immunocompromised adult. Gastroenterology 1999;116:953–958.
37. Liberski SM, Koch KL, Atnip RG, Stern RM. Ischemic gastroparesis: resolution after revascularization. Gastroenterology 1990;99:252–257.
38. Netzer P, Binek J, Hammer B. Diffuse abdominal pain, nausea and vomiting due to retroperitoneal fibrosis: a rare but often missed diagnosis. Eur J Gastroenterol Hepatol 1997;9:1005–1008.
39. Gonzalez-Rosales F, Walsh D. Intractable nausea and vomiting due to gastrointestinal mucosal metastases relieved by tetrahydrocannabinol (dronabinol). J Pain Symptom Manage 1997; 14:311–314.
40. Mathias JR, Fernandez A, Sninsky CA, Clench MH, Davis RH. Nausea, vomiting, and abdominal pain after Roux-en-Y anastomososis: motility of the jejunal limb. Gastroenterology 1985; 88:101–107.
41. Quigley EMM. Gastric and small intestinal motility in health and disease. Gastroenterol Clin North Am 1996;25:113–145.
42. Soykan I, Lin Z, Jones S, Chen J, McCallum RW. Gastric myoelectrical activity gastric emptying and correlations with dyspepsia symptoms in patients with gastroesophageal reflux. J Invest Med 1997;45:483–487.
43. Quigley EMM. Motility, heartburn and dyspepsia. Aliment Pharmacol Ther 1997;11(suppl 2):41–50.
44. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. Dig Dis Sci 1998;43:2398–2404.
45. Oh JJ, Kim CH. Gastroparesis after a presumed viral illness: clinical and laboratory features and natural history. Mayo Clin Proc 1990;65:636–642.
46. Bityutskiy LP, Soykan I, McCallum RW. Viral gastroparesis: a subgroup of idiopathic gastroparesis—clinical characteristics and long-term outcomes. Am J Gastroenterol 1997;92:1501–1504.
47. Ahn JH, Lee JH, Lee KH, Kim WK, Lee JS, Bahng H, Jung HY, Kim YS, Kim O, Kim SH. Successful treatment with ganciclovir for cytomegalovirus duodenitis following allogenic bone marrow transplantation. Korean J Int Med 1999;14:91–94.
48. Caras S, Laurie S, Cronk W, Tompkins W, Brashear R, McCallum RW. Pancreatic cancer presenting with paraneoplastic gastroparesis. Am J Med Sci 1996;312:34–36.
49. Brzana RJ, Koch KL, Bingaman S. Gastric myoelectrical activity in patients with gastric outlet obstruction and idiopathic gastroparesis. Am J Gastroenterol 1998;93:1803–1809.
50. Quigley EMM. Motility and dyspepsia. In: Johnson DA, Katz PE, Castell DO, eds. Dyspepsia. Philadelphia: ACP, 2000:79–96.
51. Quigley EMM. Symptoms and gastric function in dyspepsia—goodbye to gastroparesis. Neurogastroenterol Motil 1996;8: 273–275.
52. Stewart JJ, Wood MJ, Wood CD, Mims ME. Effects of motion sickness and anti-motion sickness drugs on gastric function. J Clin Pharmacol 1994;34:635–643.
53. Quigley EMM. Gastrointestinal dysfunction in neurological disease. Neurologist 1999;5:101–109.
54. Lee WM, Schiodt FV. Fulminant hepatic failure. In: Schiff ER, Sorrell MF, Maddrey WC, eds. Schiff's diseases of the liver. 8th ed. Philadelphia: Lippincott-Raven, 1998:879–896.
55. Sohara N, Takagi H, Abe T, Hashimoto Y, Kojima A, Takahashi H, Nagamine T, Mori M. Nausea and vomiting induced by arterial chemo-embolization in patients with hepatocellular carcinoma and the anti-emetic effect of ondansetron hydrochloride. Support Care Cancer 1999;7:84–88.
56. Atkinson K, Romano W, Prokopiu I. An unusual cause of gastroparesis—demyelinating disease of the medulla. Dig Dis Sci 1998;43:1430–1433.
57. Szilagyi A, Stern J, Armanious S, Brem S. Gastroparesis secondary to a medulloblastoma of the posterior fossa. Clin Nucl Med 1987;12:864–866.
58. Kacker V, Gupta YK. An experimental model to study intracranial hypertension-induced vomiting in conscious dogs. Methods Find Exp Clin Pharmacol 1996;18:315–320.
59. Capobianco DJ, Cheshire WP, Campbell JK. An overview of the diagnosis and pharmacologic treatment of migraine. Mayo Clin Proc 1996;71:1055–1066.
60. Pryse-Phillips WEM, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA, Robinson G, Stirling D, Worthington I. Guidelines for the diagnosis and management of migraine in clinical practice. Can Med Assoc J 1997;156:1273–1287.
61. Ferrari MD. Migraine. Lancet 1998;351:1043–1051.
62. Szilagyi A, Schipper HM, Just N. Nausea, vomiting and diarrhea: an unusual presentation of multiple sclerosis. Can J Gastroenterol 1997;11:367–370.

63. Eynon-Lewis NJ, Kitchen N, Scaravilli F, Brookes GB. Neurenteric cyst of the cerebellopontine angle: case report. Neurosurgery 1998;42:655–658.
64. Lamont EB, Savah A. An occult cause of persistent nausa and vomiting. J Emerg Med 1997;15:633–635.
65. Baloh RW. Vertigo. Lancet 1998;352:1841–1846.
66. Reason JT, Brand JJ. Motion sickness. London: Academic, 1975.
67. Kohl RL, MacDonald S. New pharmacologic approaches to the prevention of space/motion sickness. J Clin Pharmacol 1991; 31:934–946.
68. Takeda M, Morita M, Hasegawa S, Horiia A, Kibo T, Matsumaga T. Neuropharmacology of motion sickness and emesis: a review. Acta Otolaryngol 1993;501(suppl):10–15.
69. Lucot JB. Pharmacology of motion sickness. J Vestib Res 1998; 8:61–66.
70. Jennings RT. Managing space motion sickness. J Vestib Res 1998;8:67–70.
71. Reschke MF, Bloomberg JJ, Harm DL, Phloski WH, Layne C, McDonald V. Posture, locomotion, spatial orientation and motion sickness as a function of space flight. Brain Res Rev 1998;28:102–117.
72. Jarnfelt-Samside A, Samsioe G, Velinder GM. Nausea and vomiting in pregnancy: a contribution to its epidemiology. Gynecol Obstet Invest 1983;16:221–229.
73. O'Brien B, Zhou Q. Variables related to nausea and vomiting during pregnancy. Birth 1995;22:93–100.
74. Little RE, Hook EB. Maternal alcohol and tobacco consumption and their association with nausea and vomiting during pregnancy. Acta Obstet Gynecol Scand 1979;58:15–17.
75. Walsh JW, Hasler WL, Nugent CE, Owyang C. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. Am J Physiol 1996;270:G506–G514.
76. Fisher DM. The "big little problem" of post operative nausea and vomiting; do we know the answer yet? Anaesthesiology 1997; 87:1271–1273.
77. Watcha MF, White PF. Post-operative nausea and vomiting: do they matter? Eur J Anaesthesiol 1995(suppl 10):18–23.
78. Watcha MF, White PF. Post operative nausea and vomiting; its etiology, treatment and prevention. Anesthesiology 1993;78: 403–406.
79. Quinn AC, Brown JH, Wallace PG, Asbury AJ. Studies in postoperative sequelae. Nausea and vomiting—still a problem. Anaesthesia 1994;49:62–65.
80. Kenny GN. Risk factors for postoperative nausea and vomiting. Anaesthesia 1994;49:6–10.
81. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. Anesth Analg 1994;78:7–16.
82. Koivuranta M, Laara E, Snare L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia 1997;52:443–449.
83. Li BUK, Murray RD, Heitlinger LA, Robbins JL, Hayes JR. Heterogeneity of diagnoses presenting as cyclic vomiting. Pediatrics 1998;102:583–587.
84. Pfau BT, Li BUK, Murray RD, Heitlinger LA, McClung HJ, Hayes JR. Differentiating cyclic from chronic vomiting patterns in children: quantitative criteria and diagnostic implication. Pediatrics 1996;97:364–368.
85. Abu-Arefeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. J Pediatr Gastroenterol Nutr 1995; 21:454–458.
86. Boles RG, Chun M, Senadheera D, Wong LJ. Cyclic vomiting syndrome and mitochondrial DNA mutations. Lancet 1997;350: 1299–1300.
87. Pasricha PJ, Schuster MM, Saudek CD, Wand G, Ravich WJ. Cyclic vomiting: association with multiple homeostatic abnormalities and response to ketorolac. Am J Gastroenterol 1996; 91:2228–2232.
88. Ingram DA, Fulton RA, Portal RW, Aber CP. Vomiting as a diagnostic aid in acute ischaemic cardiac pain. Br Med J 1980;281: 636–637.
89. Gnecchi Ruscone T, Guzzetti S, Lombardi F, Lombardi R. Lack of association between prodromal nausea and vomiting, and specific electrocardiographic patterns of acute myocardial infarction. Int J Cardiol 1986;11:17–23.
90. Herlihy T, McIvor ME, Cummings CC, Siu CO, Alikahn M. Nausea and vomiting during acute myocardial infarction and its relation to infarct size and location. Am J Cardiol 1987;60:20–22.
91. Tyndall A, Nystrom KV, Funk M. Nausea and vomiting in patients undergoing radiofrequency catheter ablation. Am J Crit Care 1997;6:437–444.
92. Mattioli V, Calo A, Pisoni G, Anconca G, Zollino D, Brunetti P. Oral granisetron as prophylaxis for nausea and vomiting during fluorescein angiography. A multicentre, double-blind, randomised, parallel group, placebo-controlled study. Minerva Anestesiol 1998;64:553–561.
93. Prakash C, Lustman PJ, Freedland KE, Clouse RE. Tricyclic antidepressants for functional nausea and vomiting: clinical outcome in 37 patients. Dig Dis Sci 1998;43:1951–1956.
94. Koch KL. Approach to the patient with nausea and vomiting. In: Yamada T, Alpers DH, Owyang C, Powell DW, Silverstein FE, eds. Textbook of gastroenterology. 2nd ed. Philadelphia: Lippincott, 1995:731–749.
95. Schoen RE, Brandt LJ. A 19-year-old woman with unexplained vomiting. Gastroenterology 1993;104:302–309.
96. Wood JR, Camilleri M, Low PA, Malagelada JR. Brainstem tumor presenting as an upper gut motility disorder. Gastroenterology 1985;89:1411–1414.
97. Abell TL, Kim CH, Malagelada J-R. Idiopathic cyclic nausea and vomiting—a disorder of gastrointestinal motility. Mayo Clin Proc 1988;63:1169–1175.
98. Brzana RJ, Koch KL. Gastroesophageal reflux disease presenting with intractable nausea. Ann Intern Med 1997;126:704–707.
99. Ockner RK. Introduction to gastrointestinal diseases. In: Bennett JC, Plum F, eds. Cecil textbook of medicine. Philadelphia: Saunders, 1996:627–630.
100. Muraoka M, Mine K, Nakai Y, Nakagawa T. Psychogenic vomiting: the relation between patterns of vomiting and psychiatric diagnoses. Gut 1990;31:526–528.
101. Nausea and vomiting in a 69-year-old man following cholecystectomy. Am J Med 1994;96:471–481.
102. Mann SD, Danesh BJ, Kamm MA. Intractable vomiting due to a brain-stem lesion in the absence of neurological signs or raised intracranial pressure. Gut 1998;42:875–877.
103. Stanghellini V, Tosetti C, Paternico A, Barbara G, Morselli-Labate AM, Monetti N, Marengo M, Corinaldesi R. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. Gastroenterology 1996;110:1036–1042.
104. Horowitz M, Fraser RJL. Gastroparesis: diagnosis and management. Scand J Gastroenterol 1995;30(suppl 213):7–16.
105. Rothstein RD, Alavi A, Reynolds JC. Electrogastrography in patients with gastroparesis and effect of long-term cisapride. Dig Dis Sci 1993;38:1518–1524.
106. Talley NJ, Shuter B, McCrudden G, Jones M, Hoschi R, Piper DW. Lack of association between gastric emptying of solids and symptoms in non-ulcer dyspepsia. J Clin Gastroenterol 1989; 11:625–630.
107. Korson M. Metabolic etiologies of cyclic or recurrent vomiting. J Pediatr Gastroenterol Nutr 1995;21(suppl I):S15–S19.
108. Malagelada JR, Camilleri M. Unexplained vomiting: a diagnostic challenge. Ann Intern Med 1984;101:211–218.

109. Soykan, McCallum RW. Nausea, vomiting and anorexia. In: Stein JH, ed. Internal medicine. St. Louis, MO: Mosby, 1998: 2025–2030.
110. Shrake PD, Rex DK, Lappas JC, Maglinte DDT. Radiographic evaluation of suspected small bowel obstruction. Am J Gastroenterol 1991;86:175–178.
111. Herlinger H. Guide to imaging of the small bowel. Gastroenterol Clin North Am 1995;24:309–329.
112. Dooley CP, Larson AW, Stace NH, Renner IG, Valenzuela JE, Eliasoph J, Colletti PM, Halls JM, Veiner JM. Double-contrast barium meal and upper gastrointestinal endoscopy. Ann Intern Med 1984;101:538–545.
113. Cotton PB, Shorvon PJ. Analysis of endoscopy and radiography in the diagnosis, follow-up and treatment of peptic ulcer disease. Clin Gastroenterol 1984;13:383–403.
114. Brown P, Salmon PR, Burwood RJ, Knox AJ, Clendinnen BG, Read AE. The endoscopic, radiologic, and surgical findings in chronic duodenal ulceration. Scand J Gastroenterol 1978;13: 557–560.
115. Talley NJ, Phillips SF. Non-ulcer dyspepsia: potential causes and pathophysiology. Ann Intern Med 1988;108:865–879.
116. Rogers IM, Sokhi GS, Moule B, Joffe SN, Blumgart LH. Endoscopy and routine and double-contrast barium meal in diagnosis of gastric and duodenal disorders. Lancet 1976;1:901–902.
117. Levine MS. Role of the double-contrast upper gastrointestinal series in the 1990s. Gastroenterol Clin North Am 1995;24: 289–308.
118. Laufer I. Assessment of the accuracy of double contrast gastroduodenal radiology. Gastroenterology 1976;71:874–878.
119. Bhattacharya I. Evaluation and management of dyspepsia. Hosp Pract 1992;27:93–101.
120. Colin-Jones DG. Endoscopy or radiology for upper gastrointestinal symptoms? Lancet 1986;1:1022–1023.
121. Silvis SE, Nebel O, Rogers G, Sugawa C, Mandelstam P. Endoscopic complications. JAMA 1976;235:928–930.
122. Davis RE, Graham DY. Endoscopic complications. The Texas experience. Gastrointest Endosc 1979;25:146.
123. Quine MA, Bell GD, McCloy RF, Matthews HR. Prospective audit of perforation rates following upper gastrointestinal endoscopy in two regions of England. Br J Surg 1995;82:530–533.
124. Zubarik R, Eisen G, Mastropietro C, Lopez J, Carroll J, Benjamin S, Fleischer DE. Prospective analysis of complications 30 days after outpatient upper endoscopy. Am J Gastroenterol 1999; 94:1539–1545.
125. Maglinte DDT, Lappas JC, Kelvin FM, Rex D, Chernish SM. Small bowel radiography: how, when and why? Radiology 1987;163: 297–305.
126. Sanders DE. The small bowel enema: experience with 150 examinations. Am J Roentgenol 1976;127:743–751.
127. Caroline DF, Herlinger H, Laufer I, Kressel HY, Levine MS. Small-bowel enema in the diagnosis of adhesive obstructions. AJR Am J Roentgenol 1984;142:1133–1139.
128. Maglinte DDT, Lappas JC, Chernish SM, Kohne JC, Kelvin FM, Ng AC. Improved tolerance of enteroclysis by use of sedation. AJR Am J Roentgenol 1988;151:951–952.
129. Maglinte DDT, Burney BT, Miller RE. Lesions missed on small-bowel follow-through: analysis and recommendations. Radiology 1982;144:737–739.
130. Bessette JR, Maglinte DDT, Kelvin FM, Chernish SM. Primary malignant tumors in the small bowel: comparison of the small-bowel enema and conventional follow-through examination. AJR Am J Roentgenol 1989;153:741–744.
131. Minardi AJ Jr, Zibari GB, Aultman DF, McMillan RW, McDonald JC. Small-bowel tumors. J Am Coll Surg 1998;186:664–668.
132. Maglinte DD, Balthazar EJ, Kelvin FM, Megibow AJ. The role of radiology in the diagnosis of small-bowel obstruction. AJR Am J Roentgenol 1997;168:1171–1180.
133. Makanjuola D. Computed tomography compared with small bowel enema in clinically equivocal intestinal obstruction. Clin Radiol 1998;53:203–208.
134. Donckier V, Closset J, Van Gansbeke D, Zalcman M, Sy M, Houben JJ, Lambilliotte JP. Contribution of computed tomography to decision making in the management of adhesive small bowel obstruction. Br J Surg 1998;85:1071–1074.
135. Peck JJ, Milleson T, Phelan J. The role of computed tomography with contrast and small bowel follow-through in management of small bowel obstruction. Am J Surg 1999;177:375–378.
136. Suri S, Gupta S, Sudhakar PJ, Venkataramu NK, Sood B, Wig JD. Comparative evaluation of plain films, ultrasound and CT in the diagnosis of intestinal obstruction. Acta Radiol 1999;40:422–428.
137. Camilleri M, Hasler WL, Parkman HP, Quigley EMM, Soffer E. Measurement of gastroduodenal motility in the GI laboratory. Gastroenterology 1998;115:747–762.
138. Chaudhuri TK, Fink S. Gastric emptying in human disease states. Am J Gastroenterol 1991;86:533–538.
139. Choi M-G, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA, Nair KS. ^{13}C-octanoic acid breath test for gastric emptying of solids: accuracy, reproducibiltiy, and comparison with scintigraphy. Gastroenterology 1997;112:1155–1162.
140. You CH, Lee KY, Chey WY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating, and vomiting. Gastroenterology 1980;79:311–314.
141. Chen JDZ, McCallum RW. Clinical applications of electrogastrography. Am J Gastroenterol 1993;88:1324–1336.
142. Hamilton JW, Bellahsene BE, Reichelderfer M, Webster JG, Bass P. Human electrogastrograms—comparison of surface and mucosal recordings. Dig Dis Sci 1986;31:33–39.
143. Dubois A. Gastric dysrhythmias: pathophysiologic and etiologic factors. Mayo Clin Proc 1989;64:246–250.
144. Chen JDZ, Lin Z, Pan J, McCallum RW. Abnormal gastric myoelectric activity and delayed gastric emptying in patients with symptoms suggestive of gastroparesis. Dig Dis Sci 1996;41: 1538–1545.
145. Chen J, McCallum RW. Gastric slow wave abnormalities in patients with gastroparesis. Am J Gastroenterol 1992;87:477–482.
146. Bortolotti M, Pinotti R, Barbara L. Gastric myoelectric activity in patients with chronic idiopathic gastroparesis (abstr). Gastroenterology 1988;95:857.
147. Koch KL, Stern RM, Stewart WR, Vasey MW. Gastric emptying and gastric myoelectric activity in patients with diabetic gastroparesis: effect of long-term domperidone treatment. Am J Gastroenterol 1989;84:1069–1074.
148. Koch Kl, Stern KM, Vasey M, Botti JJ, Creasy GW, Dwyer A. Gastric dysrhythmias and nausea of pregnancy. Dig Dis Sci 1990;35:961–968.
149. Stern RM, Koch KL, Stewart WR. Spectral analysis of tachygastria recorded during motion sickness. Gastroenterology 1987;92:92–97.
150. Malagelada JR. Where do we stand on gastric motility? Scand J Gastroenterol 1990;25(suppl 175):42–51.
151. Vantrappen G, Jannssens J, Hellemans J, Ghoos Y. The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest 1977; 59:1158–1166.
152. Thompson DG, Wingate DL, Archer L, Benson MJ, Green WJ, Hardy RJ. Normal patterns of human upper small bowel motor activity recorded by prolonged radiotelemetry. Gut 1980;21: 500–506.
153. Ouyang A, Sunshine AG, Reynolds JC. Caloric content of a meal affects duration but not contractile pattern of duodenal motility in man. Dig Dis Sci 1989;34:528–536.

154. Kerlin P. Postprandial antral hypomotility in patients with idiopathic nausea and vomiting. Gut 1989;30:54–59.
155. Camilleri M. Study of human gastroduodenojejunal motility—applied physiology in clinical practice. Dig Dis Sci 1993;38: 785–794.
156. Summers RW, Anuras S, Green J. Jejunal manometry patterns in health, partial intestinal obstruction, and pseudoobstruction. Gastroenterology 1983;85:1290–1300.
157. Malagelada JR, Stanghellini V. Manometeric evaluation of functional upper gut symptoms. Gastroenterology 1985;88:1223–1231.
158. Wingate DL. Small intestine. In: Schuster MM. Atlas of gastrointestinal motility in health and disease. Baltimore, MD: Williams & Wilkins, 1993:177–214.
159. Quigley EMM. Intestinal manometry—technical advances; clinical limitations. Dig Dis Sci 1992;37:10–13.
160. Quigley EMM, Deprez P, Hellstrom P, Husebye E, Soffer EE, Stanghellini V, Summers RW, Wilmer A, Wingate DLW. Ambulatory intestinal manometry: a consensus report on its clinical role. Dig Dis Sci 1997;42:2395–2400.
161. Quigley EMM. Enteric neuropathology—recent advances and implications for clinical practice. Gastroenterologist 1997;5: 233–241.
162. Soffer E, Thongsawat S. Clinical value of duodenojejunal manometry. Dig Dis Sci 1996;41:859–863.
163. Stanghellini V, Camilleri M, Malagelada JR. Chronic idiopathic intestinal pseudo-obstruction: clinical and intestinal manometric findings. Gut 1987;28:5–12.
164. Frank JW, Sarr MG, Camilleri M. Use of gastroduodenal manometry to differentiate mechanical and functional intestinal obstruction: an analysis of clinical outcome. Am J Gastroenterol 1994;89:339–344.
165. Byrne KG, Quigley EMM. Antroduodenal manometry: an evaluation of an emerging methodology. Dig Dis 1997;15(suppl 1): 53–63.
166. Evans RW. Diagnostic testing for the evaluation of headaches. Neurol Clin 1995;14:1–26.
167. Schwartz RB. Neuroradiology of brain tumors. Neurol Clin 1995; 13:723–756.
168. Swanson DW, Swenson WM, Huizenga KA, Nelson SJ. Persistent nausea without organic cause. Mayo Clin Proc 1976;51: 257–262.
169. Golding JF, Stott JR. Comparison of the effects of a selective muscarinic receptor antagonist and hyoscine (scopolamine) on motion sickness, skin conductance and heart rate. Br J Clin Pharmacol 1997;432:633–637.
170. Pingree BJ, Pethybridge RJ. A comparison of the efficacy of cinnarizine with scopolamine in the treatment of seasickness. Aviat Space Environ Med 1994;65:597–605.
171. Weinstein SE, Stern RM. Comparison of marezine and dramamine in preventing symptoms of motion sickness. Aviat Space Environ Med 1997;68:890–894.
172. Doweck I, Gordon CR, Spitzer O, Melamed Y, Shupak A. Effect of cinnarizine in the prevention of seasickness. Aviat Space Environ Med 1994;65:606–609.
173. Davis JR, Jennings RT, Beck BG, Bagian JP. Treatment efficacy of intramuscular promethazine for space sickness. Aviat Space Environ Med 1993;64:230–233.
174. Wood CD, Stewart JJ, Wood MJ, Mims M. Effectiveness and duration of intramuscular anti-motion sickness medications. J Clin Pharmacol 1992;32:1008–1012.
175. Bond CM. Comparison of buccal and oral prochlorperazine in the treatment of dizziness associated with nausea and/or vomiting. Curr Med Res Opin 1998;14:203–212.
176. Lackner JR, Graybiel A. Use of promethazine to hasten adaptation to provocative motion. J Clin Pharmacol 1994;34:644–651.
177. Pfaffenrath V, Rehm M. Migraine in pregnancy: what are the safest treatment options? Drug Safety 1998;19:383–388.
178. Sallam SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer. A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med 1980;302:135–138.
179. Robbins EL, Magel JD. Haloperidol parenterally for treatment of vomiting and nausea from gastrointestinal disorders in a group of geriatric patients: double-blind, placebo-controlled study. J Am Geriatr Soc 1975;23:38–41.
180. Talley NJ. Review article: 5-hydroxytryptamine agonists and antagonists in the modulation of gastrointestinal motility and sensation—clinical implications. Aliment Pharmacol Ther 1992;6:273–290.
181. Bodis S, Alexander E III, Kooy H, Loeffler JS. The prevention of radiosurgery-induced nausea and vomiting by ondansetron: evidence of a direct effect on the central nervous system chemoreceptor trigger zone. Surg Neurol 1994;42:249–252.
182. Barone JA. Domperidone: a peripherally acting dopamine 2-receptor antagonist. Ann Pharmacother 1999;33:429–440.
183. McCallum RW, Albibi R. Metoclopramide: pharmacology and clinical application. Ann Intern Med 1983;98:86–92.
184. Parkes JD. Domperidone and Parkinson's disease. Clin Neuropharmacol 1986;9:517–532.
185. Navari RM, Reinhardt RR, Gralla RJ, Kris MG, Hesketh PJ, Khojasteh A, Kindler H, Grote TH, Pendergrass K, Grunberg SM, Carides AD, Gertz BJ. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. N Engl J Med 1999;340:190–195.
186. Quigley EMM. The clinical pharmacology of motility disorders: the perils (and pearls) of prokinesia. Gastroenterology 1994; 106:1112–1114.
187. Malagelada JR, Rees WDW, Mazzotta LJ, Go VLW. Gastric motor abnormalities in diabetic and post-vagotomy gastroparesis: effect of metoclopramide and bethanechol. Gastroenterology 1980;78:286–293.
188. Ramirez B, Richter JE. Review article: promotility drugs in the treatment of gastroesophageal reflux disease. Aliment Pharmacol Ther 1993;7:5–20.
189. Hawkey CJ. The place of cisapride in therapeutics: an interim verdict. Aliment Pharmacol Ther 1991;5:351–356.
190. Heading RC, Wood JD. Gastrointestinal dysmotility. Focus on cisapride. Raven Health Care Comm 1992.
191. Hill S, Evangelista J, Pizza A. Proarrhythmia associated with cisapride in children. Pediatrics 1998;101:1053–1056.
192. Abell TL, Camilleri M, DiMagno EP, Hench VS, Zinsmeister AR, Malagelada JR. Long-term efficacy of oral cisapride in symptomatic upper gut dysmotility. Dig Dis Sci 1991;36:621–626.
193. Wehrmann T, Lembcke B, Caspary WF. Influence of cisapride on antroduodenal motor function in healthy subjects and diabetics with autonomic neuropathy. Aliment Pharmacol Ther 1991;5: 599–608.
194. Camilleri M, Malagelada JR, Abell TL, Brown ML, Hench V, Zinsmeister AR. Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudo-obstruction. Gastroenterology 1989;96:704–712.
195. McHugh S, Lico S, Diamant NE. Cisapride versus metoclopramide: an acute study in diabetic gastroparesis. Dig Dis Sci 1992;37:997–1001.
196. Richards RD, Valenzuela JA, Davenport KS, Fisher KLK, McCallum RW. Objective and subjective-results of a randomized, double-blind, placebo-controlled trial using cisapride to treat gastroparesis. Dig Dis Sci 1993;38:811–816.
197. Camilleri M, Balm RK, Zinsmeister AR. Determinants of response to a prokinetic agent in neuropathic chronic intestinal motility disorder. Gastroenterology 1994;106:916–923.
198. Tack J, Janssens J, Vantrappen G, Peeters T, Annese V, De-

poortere I, Muls E, Bouillon R. Effect of erythromycin on gastric motility in controls and in diabetic gastroparesis. Gastroenterology 1992;103:72–79.
199. Fraser R, Shearer T, Fuller J, Horowitz M, Dent J. Intravenous erythromycin overcomes small intestinal feedback on antral, pyloric and duodenal motility. Gastroenterology 1992;103: 116–119.
200. Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, DeRoo M, Muls E, Bouillon R. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. N Engl J Med 1990; 322:1028–1031.
201. Weber FH, Richards RD, McCallum RW. Erythromcyin: a motilin agonist and gastrointestinal prokinetic agent. Am J Gastroenterol 1993;88:485–490.
202. Keshavarzian A, Isaac RM. Erythromycin accelerates gastric emptying of indigestible solids and transpyloric migration of the tip of an enteral feeding tube in fasting and fed states. Am J Gastroenterol 1993;88:193–197.
203. Mantides A, Xynos E, Chrysos E, Georgopoulos N, Vassilakis JS. The effect of erythromycin in gastric emptying of solids and hypertonic liquids in healthy subjects. Am J Gastroenterol 1993;88:198–202.
204. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol 1993;88: 203–207.
205. Fiorucci S, Distrutti E, Bassotti G, Gerli R, Chiucchiu S, Betti C, Saritucci L, Morelli A. Effect of erythromycin administration on upper gastrointestinal motility in scleroderma patients. Scand J Gastroenterol 1994;29:807–813.
206. Camilleri M. The current role of erythomycin in the clinical management of gastric emptying disorders. Am J Gastroenterol 1993;88:169–171.
207. McCallum RW, Chen JDZ, Lin Z, Schirmer BD, Williams RD, Ross RA. Gastric pacing improves emptying and symptoms in patients with gastroparesis. Gastroenterology 1998; 114:456–461.
208. Tougas G, Huizinga JD. Gastric pacing as a treatment for intractable gastroparesis: shocking news? Gastroenterology 1998; 114:598–601.
209. Tramer MR, Phillips C, Reynolds DJ, McQuay HJ, Moore RA. Cost-effectiveness of ondansetron for post-operative nausea and vomiting. Anaesthesia 1999;54:226–234.
210. Divatia JV, Vaidya JS, Badwe RA, Hawaldar RW. Omission of nitrous oxide during anesthesia reduces the incidence of postoperative nausea and vomiting. A meta-analysis. Anesthesiology 1996;85:1055–1062.
211. Gan TJ, Ginsberg B, Grant AP, Glass PS. Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology 1996;85:1036–1042.
212. McKenzie R, Riley TJ, Tantisira B, Hamilton DL. Effect of propofol for induction and ondansetron with or without dexamethasone for the prevention of nausea and vomiting after major gynecologic surgery. J Clin Anesth 1997;9:15–20.
213. Scholz J, Hennes HJ, Steinfath M, Farber L, Schweiger C, Dick W, Schulte am Esch J. Tropisetron or ondansetron compared with placebo for prevention of post-operative nausea and vomiting. Eur J Anaesthesiol 1998;15:676–685.
214. Morris RW, Aune H, Feiss P, Hanson A, Hasselstrom L, Maltby JR, Rocke DA, Rozenberg B, Rust M, Cohen LA. International, multicentre, placebo-controlled study to evaluate the effectiveness of ondansetron vs. metoclopramide in the prevention of post-operative nausea and vomiting. Eur J Anaesthesiol 1998; 15:69–79.
215. Diemunsch P, Korttila K, Leeser J, Helmers JH, Wilkey B, Nave S, Radke AJ, Hahne WF, Brown RA. Oral dolasetron mesylate for prevention of post-operative nausea and vomiting: a multicenter, double-blind, placebo-controlled study. The Oral Dolasetron PONV Prevention Study Group. J Clin Anesth 1998;10: 145–152.
216. Koivuranta M, Laara E, Ranta P, Ravaska P, Alahuhta S. Comparison of ondansetron and droperidol in the prevention of post-operative nausea and vomiting after laparoscopic surgery in women. A randomised, double-blind, placebo-controlled trial. Acta Anaesthesiol Scand 1997;41:1273–1279.
217. Warriner CB, Knox D, Belo S, Cole C, Finegan BA, Perreault L. Prophylactic oral dolasetron mesylate reduces nausea and vomiting after abdominal hysterectomy. The Canadian Dolasetron Study Group. Can J Anaesth 1997;44:1167–1173.
218. Korttila K, Clergue F, Leeser J, Feiss P, Olthoff D, Payeur-Michel C, Wessel P, Nave S, Hahne W, Brown R. Intravenous dolasetron and ondansetron in prevention of post-operative nausea and vomiting: a multicenter, double-blind, placebo-controlled study. Acta Anaesthesiol Scand 1997;41:914–922.
219. Graczyk SG, McKenzie R, Kallar S, Hickok CB, Melson T, Morrill B, Hahne WF, Brown RA. Intravenous dolasetron for the prevention of post-operative nausea and vomiting after out-patient laparoscopic gynecologic surgery. Anesth Analg 1997;84:325–330.
220. Wilson AJ, Diemunsch P, Lindeque BG, Scheinin H, Helbo-Hansen HS, Kroeks MV, Kong KL. Single-dose i.v. granisetron in the prevention of post-operative nausea and vomiting. Br J Anaesth 1996;76:515–518.
221. Capouet V, DePauw C, Vernet B, Ivens D, Derijcke V, Versichelen L, van Aken H, Ickx B, Ritter L, Hulstaert F. Single dose i.v. tropisetron in the prevention of post-operative nausea and vomiting after gynaecological surgery. Br J Anaesth 1996;76: 54–60.
222. Paech MJ, Pavy TJ, Evans SF. Single-dose prophylaxis for postoperative nausea and vomiting after major abdominal surgery: ondansetron versus droperidol. Anaesth Intens Care 1995;23: 548–554.
223. Desilva PH, Darvish AH, McDonald SM, Cronin MK, Clark K. The efficacy of prophylactic ondansetron, droperidol, perphenazine, and metoclopramide in the prevention of nausea and vomiting after major gynecologic surgery. Anesth Analg 1995;81:139–143.
224. Fortney JT, Gan TJ, Graczyk S, Wetchler B, Melson T, Khalil S, McKenzie R, Parrillo S, Glass PS, Moote C, Wermeling D, Parasuraman TV, Duncan B, Creed MR. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. Anesth Analg 1998;86: 731–738.
225. Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of post-operative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997;87:1277–1289.
226. Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. A quantitative systemic review of ondansetron in treatment of established post-operative nausea and vomiting. BMJ 1997;314:1088–1092.
227. Taylor AM, Rosen M, Diemunsch PA, Thorin D, Houweling PL. A double-blind, parallel-group, placebo-controlled, dose-ranging, multicenter study of intravenous granisetron in the treatment of post-operative nausea and vomiting in patients undergoing surgery with general anesthesia. J Clin Anesth 1997;9:658–663.
228. Alon E, Buchser E, Herrera E, Christiaens F, De Pauw C, Ritter L, Hulstaert F, Grimaudo V. Tropisetron for treating established

post-operative nausea and vomiting: a randomized, double-blind, placebo-controlled study. Anesth Analg 1998;86:617–623.
229. Munstedt K, Muller H, Blauth-Eckmeyer E, Stenger K, Zygmunt M, Vahrson H. Role of dexamethasone dosage in combination with 5-HT3 antagonists for prophylaxis of acute chemotherapy-induced nausea and vomiting. Br J Cancer 1999;79:637–639.
230. Perez EA. Use of dexamethasone with 5-HT3-receptor antagonists for chemotherapy-induced nausea and vomiting. Sci Am 1998;4:72–77.
231. Gregory RE, Ettinger DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. Drugs 1998;55:173–189.
232. Peterson C, Hursti TJ, Borjeson S, Avall-Lundqvist E, Fredrikson M, Furst CJ, Lomberg H, Steineck G. Single high-dose dexamethasone improves the effect of ondansetron on acute chemotherapy-induced nausea and vomiting but impairs the control of delayed symptoms. Support Care Cancer 1996;4:440–446.
233. The Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. N Engl J Med 1995;332:1–5.
234. Osoba D, Warr D, Fitch MI, Nakashima L, Warren B. Guidelines for the optimal management of chemotherapy-induced nausea and vomiting: a consensus. Can J Oncol 1995;5:381–400.
235. Sorbe BG, Hogberg T, Glimelius B, Schmidt M, Wernstedt L, Andersson H, Hansen O, Sorensen BT, Raisanen I. Navoban (tropisetron) alone and in combination with dexamethasone in the prevention of chemotherapy-induced nausea and vomiting: the Nordic experience. The Nordic Antiemetic Trial Group. Anticancer Drugs 1995;6:31–66.
236. Del Favero A, Roila F, Tonato M. Reducing chemotherapy-induced nausea and vomiting. Current perspectives and future possibilities. Drug Safety 1993;9:410–428.
237. Yarker YE, McTavish D. Granisetron. An update of its therapeutic use in nausea and vomiting induced by antineoplastic therapy. Drugs 1994;48:761–793.
238. Whitmore JB, Kris MG, Hesketh PJ, Grote TH, DuBois DM, Cramer MB, Hahne WF. Rationale for the use of a single fixed intravenous dolasetron dose for the prevention of cisplatin-induced nausea and vomiting. Pooled analysis of 14 clinical trials. Support Care Cancer 1998;6:473–478.
239. Lofters WS, Pater JL, Zee B, Dempsey E, Walde D, Moquin JP, Wilson K, Hoskins P, Guevin RM, Verma S, Navari R, Krook JE, Hainsworth J, Palmer M, Chin C. Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy. J Clin Oncol 1997;15:2966–2973.
240. Pater JL, Lofters WS, Zee B, Dempsey E, Walde D, Moquin JP, Wilson K, Hoskins P, Guevin RM, Verma S, Navari R, Krook JE, Hainsworth J, Palmer M, Chin C. The role of the 5-HT3 antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Ann Oncol 1997;8:181–185.
241. Gebbia V, Testa A, Valenza R, Cannata G, Tirrito ML, Gebbia N. Oral granisetron with or without methylprednisolone versus metoclopramide plus methylprednisolone in the management of delayed nausea and vomiting induced by cisplatin-based chemotherapy. A prospective randomized trial. Cancer 1995;76:1821–1828.
242. Hulstaert F, Van Belle S, Bleiberg H, Canon JL, Dewitte M, Buyse M, De Keyser P, Westelinck KJ. Optimal combination therapy with tropisetron in 445 patients with incomplete control of chemotherapy-induced nausea and vomiting. J Clin Oncol 1994;12:2439–2446.
243. Gebbia V, Cannata G, Testa A, Curto G, Valenza R, Cipolla C, Latteri MA, Gebbia N. Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. Results of a prospective randomized trial. Cancer 1994;74:1945–1952.
244. Cubeddu LX, Pendergrass K, Ryan T, York M, Burton G, Meshad M, Galvin D, Ciociola AA. Efficacy of oral ondansetron, a selective antagonist of 5-HT_3 receptors, in the treatment of nausea and vomiting associated with cyclophosphamide-based chemotherapies. Ondansetron Study Group. Am J Clin Oncol 1994;17:137–146.
245. Latreille J, Pater J, Johnston D, Laberge F, Stewart D, Rusthoven J, Hoskins P, Findlay B, McMurtrie E, Yelle L, Williams C, Walde D, Ernst S, Dhaliwal H, Warr D, Shepherd F, Mee D, Nishimura L, Osoba D, Zee B. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. J Clin Oncol 1998;16:1174–1178.
246. Munstedt K, Wunderlich I, Blauth-Eckmeyer E, Zygmunt M, Vahrson H. Does dexamethasone enhance the efficacy of alizapride in cis-platinum–induced delayed vomiting and nausea? Oncology 1998;55:293–299.
247. Malik IA, Khan WA, Qazilbash M, Ata E, Butt A, Khan MA. Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin. A prospective randomized trial. Am J Clin Oncol 1995;18:170–175.
248. Morrow GR, Dobkin PL. Anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment: prevalence, etiology and behavioral intervention. Clin Psychol Rev 1988;8:517–556.
249. Spitzer TR, Bryson JC, Cirenza E, Foelber R, Wallerstadt M, Stout C, Kunka RL, Plagge PB, Dubois A. Randomized double-blind, placebo-controlled evaluation of oral ondansetron in the prevention of nausea and vomiting associated with fractionated total-body irradiation. J Clin Oncol 1994;12:2432–2438.
250. Bey P, Wilkinson PM, Resbeut M, Bourdin S, Le Floch O, Hahne W, Claverie N. A double-blind, placebo-controlled trial of i.v. dolasetron mesilate in the prevention of radiotherapy-induced nausea and vomiting in cancer patients. Support Care Cancer 1996;4:378–383.
251. Sykes AJ, Kiltie AE, Stewart AL. Ondansetron versus a chlorpromazine and dexamethasone combination for the prevention of nausea and vomiting: a prospective, randomised study to assess efficacy, cost effectiveness and quality of life following single-fraction radiotherapy. Support Care Cancer 1997;5:500–503.
252. Tramer MR, Reynolds DJ, Stoner NS, Moore RA, McQuay HJ. Efficacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: a quantitative systematic review. Eur J Cancer 1998;34:1836–1844.
253. Mystakidou K, Befon S, Liossi C, Vlachos L. Comprison of tropisetron and chlorpromazine combinations in the control of nausea and vomiting of patients with advanced cancer. J Pain Symptom Management 1998;15:176–184.
254. Nelson-Piercy C. Treatment of nausea and vomiting in pregnancy. When should it be treated and what can be safely taken? Drug Safety 1998;19:155–164.
255. Broussard CN, Richter JE. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am 1998;27:123–151.
256. O'Brien B, Relyea MJ, Taerum T. Efficacy of P6 acupressure in the treatment of nausea and vomiting during pregnancy. Am J Obstet Gynecol 1996;174:708–715.
257. Belluomini J, Litt RC, Lee KA, Katz M. Acupressure for nausea and vomiting of pregnancy: a randomized, blinded study. Obstet Gynecol 1994;84:245–248.
258. Ylikorkala O, Kauppila A, Ollanketo ML. Intramuscular ACTH or

placebo in the treatment of hyperemesis gravidarum. Acta Obstet Gynecol Scand 1979;58:453–455.
259. Safari HR, Fassett MJ, Souter IC, Alsulyman OM, Goodwin TM. The efficacy of methylprednisolone in the treatment of hyperemesis gravidarum: a randomized, double-blind, controlled study. Am J Obstet Gynecol 1998;179:921–924.
260. Fischer-Rasmussen W, Kjaser SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 1991;38:19–24.
261. Sullivan CA, Johnson CA, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;175:1565–1568.
262. van de Ven, Cosmas JM. Nasogastric enteral feeding in hyperemesis gravidarum. Lancet 1997;349:445–446.

Address requests for reprints to: Chair, Clinical Practice and Practice Economics Committee, AGA National Office, c/o Membership Department, 7910 Woodmont Avenue, 7th Floor, Bethesda, Maryland 20814. Fax: (301) 654-5920.

The Clinical Practice and Practice Economics Committee acknowledges the following individuals, whose critiques of this review paper provided valuable guidance to the authors: Robert Hammer, M.D., Ken Koch, M.D., and Joseph Murray, Ph.D.